ASSESSMENT OF FATIGUE AND OTHER EXTRA-PULMONARY MANIFESTATIONS IN PATIENTS DIAGNOSED WITH SARCOIDOSIS.

ASSESSMENT OF FATIGUE AND OTHER EXTRA-PULMONARY MANIFESTATIONS IN PATIENTS DIAGNOSED WITH SARCOIDOSIS.

- A prospective observational study in a south indian tertiary care centre

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE M.D. TUBERCULOSIS AND RESPIRATORY MEDICINE EXAMINATION OF THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI TO BE HELD IN APRIL 2015.

DECLARATION

This is to declare that this dissertation titled **ASSESSMENT OF FATIGUE AND OTHER EXTRA-PULMONARY MANIFESTATIONS IN PATIENTS DIAGNOSED WITH SARCOIDOSIS –** a prospective observational study in a south indian tertiary care centre is my original work done in partial fulfilment of rules and regulations for MD TUBERCULOSIS AND RESPIRATORY MEDICINE examination of the Tamil Nadu Dr.M.G.R Medical University, Chennai to be held in April 2015.

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CERTIFICATE:

This is to certify that the study entitled 'TO ASSESS THE PREVALENCE OF FATIGUE AND OTHER EXTRA-PULMONARY MANIFESTATIONS IN PATIENTS WITH SARCOIDOSIS' is a bonafide work of Dr. Immanuel Subash, in fulfillment of the rules and regulations for the M.D. Branch-XVII (Tuberculosis and Respiratory medicine) Degree Examination of the Tamil Nadu Dr. M.G.R University, Chennai, to be conducted in April 2015.

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assessment of fatigue and other extra-pulmonary manifestations in patients diagnosed with sarcoidosis

ORIGINALITY REPORT

2%	1%	2%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

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IRB APPROVAL

OFFICE OF RESEARCH
INSTITUTIONAL REVIEW BOARD
CHRISTIAN MEDICAL COLLEGE,
BAGAYAM, VELLORE 632002, TAMIL NADU, INDIA

Ref: FG/8592/12/2013

March 04, 2014

The Treasurer
Christian Medical College,
Vellore.

Dear Mr. Denzil,

Sub: **Fluid Research grant project**:
Assessment of fatigue and other extra-pulmonary manifestations in patients diagnosed with sarcoidosis.
Dr. Immanuel Subash. G, PG Registrar, Pulmonary Medicine, Dr. D. J. Christopher, Professor, Dr. Balamugesh T, Professor, Pulmonary Medicine.

Ref: IRB Min. No. 8592 dated 04.12.2013

The Institutional Review Board at its meeting held on December 4th 2013 vide IRB Min. No. **8592** accepted the project *for 30,000 INR (Rupees Thirty Thousand only) will be granted for1 year. If overspent the excess should be debited form the respective departmental or Special funds.* Kindly arrange to transfer the sanctioned amount to a separate account to be operated by Dr. Immanuel Subash. G and Dr. D. J. Christopher.

Yours sincerely,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD.,MNAMS.,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
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File

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THESIS ABSTRACT

Title:

To assess prevalence of fatigue and other extra-pulmonary manifestations in patients with Sarcoidosis

Department: Pulmonary Medicine

Name of candidate: Dr Immanuel Subash G

Degree and Subject: MD Pulmonary medicine

Name of the Guide: Dr D J Christopher

Objectives:

2 objectives of the study:

Primary objective: To assess the prevalence of fatigue with the help of FAS (Fatigue assessment scale)in all patents with Histo-pathologically proven sarcoidosis, both old and new, treatment naïve and on treatment, in the department of Pulmonary Medicine.

Secondary objective: Secondary objective of the study was to observe and present the prevalence of other extra-pulmonary manifestations in the same cohort.

Methods:

We included all patients in our department with the diagnosis of Sarcoidosis, which was proven histo-pathologically. Both newly diagnosed and patients who were on treatment were included. They were asked to fill in a Quality of life questionnaire – FAS (Fatigue assessment scale), which has been validated for use in patients with sarcoidosis to assess fatigue. A score of more than 21 was considered to be significant for fatigue. For assessing other extra-pulmonary manifestations basic screening tests which were done as part of

routine work up was used, Ophthalmological and Dermatological screening was done for all of them.

Results:

We included 75 patients in our study. We found fatigue as a symptom with the help of FAS more than 21 in 73.3% of patients. In newly diagnosed patients prevalence was 85.7% compared to old patients in who it was 66%. Patients on steroids had 9% higher risk of having fatigue, but statistically it was not found to be significant (odd's ratio; 0.98, p value; 0.752). There was no significant difference statistically in age or female sex – odd's ratio of 0.99 and 1.09 respectively. Assessing other extra-pulmonary manifestations we found highest prevalence in Eye and Skin with 26% and 20% respectively. Other organs involved in decreasing order of prevalence were Liver (13%), Bone/Joint/Muscle (10.6%), Spleen (9.3%), Calcium/Kidney (6.6%), Brain (4%), ENT (4%), Heart (1.3%), and Parotid gland (1.3%).

INTRODUCTION:

Sarcoidosis is a multi-system disease of unknown aetiology which is typically characterised by presence of non-caseating granulomas in the organs which are involved. Sarcoidosis term comes from the Greek words "Sark" and "oid," meaning flesh-like. Sarcoidosis typically affects the lungs in 90% of patients(1), presenting as mediastinal adenopathy , Pulmonary infiltrates, interstitial lung disease, it is also commonly known to involve other organs notably skin and eyes. Sarcoidosis can involve any organ like liver, spleen, brain, heart or any other organ. Sarcoidosis may simultaneously affect 2 or more organs. It is important to identify all the organs involved at the time of diagnosis for treatment and follow up of the patient.

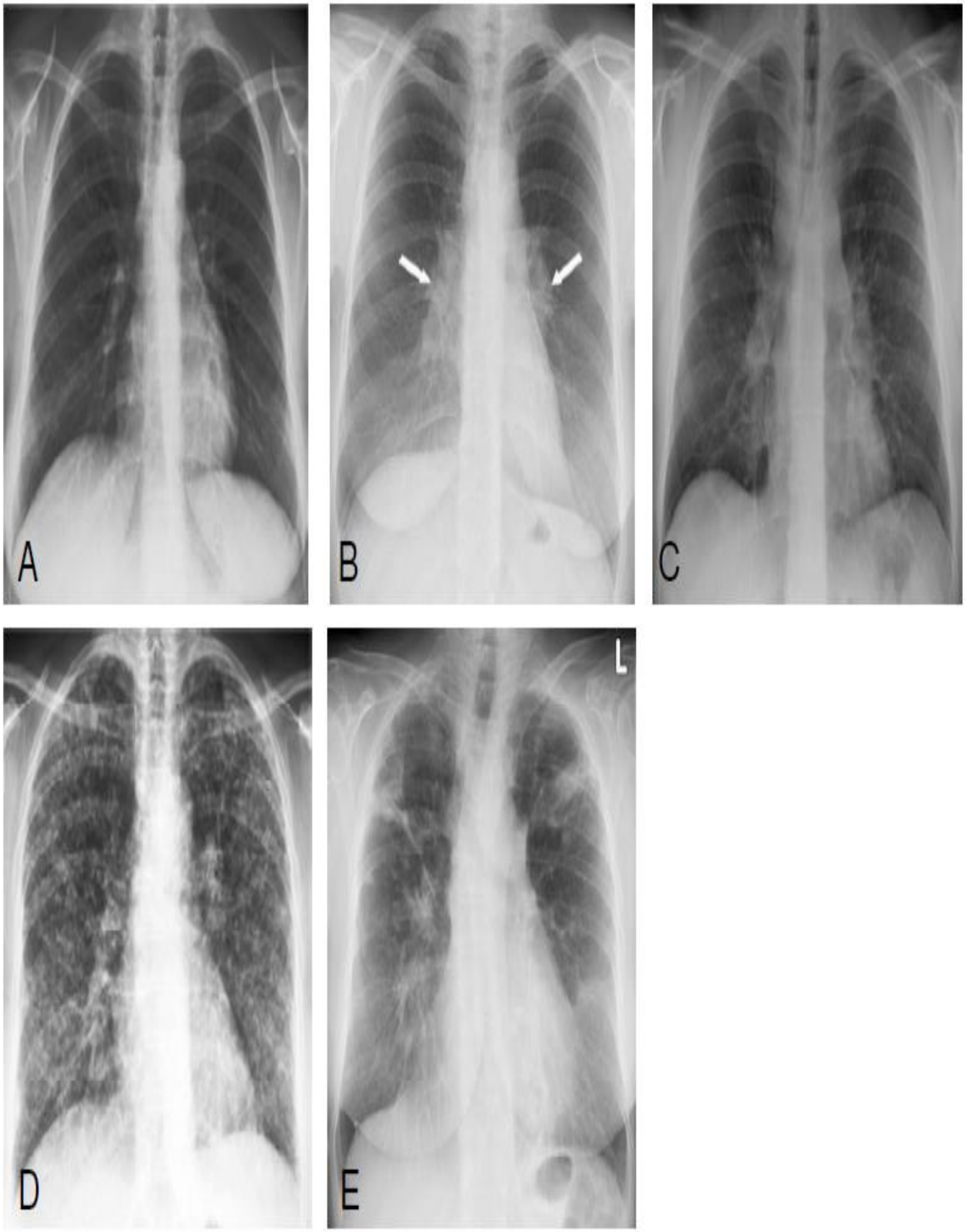
Sarcoidosis is a diagnosis made on the basis of a multi-disciplinary approach including an apt clinical picture with correlating radiological findings and proven histo-pathologically from the organ involved. Clinically patients with Sarcoidosis present with symptoms in concordance with the organ involved. The most common organ being involved with Sarcoidosis is the lung they present with symptoms of cough, breathlessness and chest pain. They may also present with other symptoms like weight loss, loss of appetite, fatigue. In few patients Sarcoidosis may be identified on a Chest x-ray done for some other reason. Patients with Sarcoidosis have extra-thoracic involvement in up to 30% of cases and may present with organ specific symptoms before pulmonary manifestations.

Radiologically Sarcodosis commonly affects the hilar and mediastinal lymphadenopathy with or without parenchymal infiltrates. Radiological classification at the time of diagnosis has been found to be important in follow up of patients with sarcoidosis. Chest x-ray might be the clue to suspicion in a patient. Sarcoidosis must always be considered as a differential in a patient presenting with cough, breathlessness and other symptoms like fatigue.

Following is the most accepted classification world-side for sarcoidosis which can be used with ease in a primary health care hospital.

Radiological classification of Sarcoidosis:

A) Stage 0: Normal Chest radiograph
B) Stage 1: Bilateral hilar adenopathy (Indicated by arrows)
C) Stage 2: Bilateral hilar adeopathy with parenchymal infiltrates
D) Stage 3: Evidence of reticular opacities with shrinking hilar lymph nodes
E) Stage 4: Evidence of reticular opacities with fibrosis and volume loss


A
B
C
D
E
L

HRCT done to characterise the pattern of involvement may show any of the following:

●Hilar and mediastinal lymphadenopathy

●Beaded or irregular thickening of the bronchovascular bundles

●Nodules along bronchi, vessels, and subpleural regions

●Bronchial wall thickening

●Ground glass opacification

●Parenchymal masses or nodular consolidation, occasionally with cavitation

●Parenchymal bands

●Cysts

●Fibrosis with distortion of the lung architecture and traction bronchiectasis

Pulmonary function testing commonly shows restrictive lung defect, in 20% of cases it may present with an obstructive defect or a mixed defect(2)

Sarcoidosis is typically characterised by presence of non caseating granulomatous inflammation demonstrated from a tissue from the organ involved(3), it is important to exclude other common causes of granulomatous inflammation which can be infectious like tuberculosis or fungal infections like histoplasmosis. Non-infectious causes of granulomatous inflammation other than Sarcoidosis are Wegener's granulomatosis, Hypersensitivity pneumonitis, Aspiration pneumonia(4).

Sarcoidosis is not as rare as it is thought to be (2), looking at studies which have been mentioned in the review of literature we found that Sarcoidosis is known to cause significant fatigue affecting quality of life of patients diagnosed with the same.

The aim of our study was to calculate the prevalence of fatigue in patients who are diagnosed with pulmonary sarcoidosis. We also looked to observe and present the prevalence of other extra-pulmonary manifestations in the same cohort of patients.

Treatment of sarcoidosis:

Not all patients with sarcoidosis will require treatment. Therapy is indicated in patients in pulmonary sarcoidosis only in the following circumstances:

Bothersome symptoms – breathlessness, cough

Worsening radiological features

Rapid worsening lf lung function as indicated by Pulmonary function testing

It is important to identify at the time of diagnosis and only treat patients who require treatment as per guidelines.

Goals of treatment in a patient with sarcoidosis are(5):

Control and prevent organ damage

Relief from symptoms

Improve quality of life

A multi- disciplinary approach is recommended for diagnosis before intitiation of treatment. Pulmonologist, radiologist and pathologist should agree with the diagnosis of sarcoidosis before starting a patient on treatment.

Patients with extra-pulmonary manifestations also demand management by the concerned specialist rather than the pulmonologist for the concerned organ involvement.

Treatment options:

To treat sarcoidosis, pharmacotherapies which have been tried are the following(5):

- Corticosteroids
- Hydroxychloroquine
- Methotrexate
- Azathioprine
- Leflunomide
- Mycophenolate
- Infliximab
- Adalimumab

Corticosteroids have been the mainstay of treatment. They act by their anti-inflammatory property by their effect on the granulomas.

Corticosteroids have been found to be useful in sarcoidosis, but adverse effects should always be kept in mind before starting a patient on sarcoidosis. Patient should be taken into confidence before inception of therapy. He/she should understand all the side effects including weight gain, decreased bone mineral density, increased blood sugars and increased blood pressures after initiating therapy. They should be advised to be screened regularly for these effects of steroids. Other agents mentioned above should be used only if there is failure of treatment.

Epidemiology:

Sarcoidosis is one of the rare diseases. Here is the known epidemiology of Sarcoidosis worldwide and in India.

World-wide:

Epidemiology of sarcoidosis as per various studies range from 5- 40 per 1,00,00 people.(6) with variation among Europeans, Americans, Japanese and Afro-Americans. In some areas it can be as high as 640 per 1,00,00 people(7).

Prevalence of sarcoidosis has been found to be slightly more in females compared to males(8)

India:

In India the prevalence of Sarcodiosis varies from 10-150 according to the available data.(9) (10),

AIM AND OBJECTIVES:

Aim –

Assessment of fatigue and other extra-pulmonary manifestations in patients

diagnosed with Pulmonary Sarcoidosis

Objectives –

Primary:

Prevalence of Fatigue in all patients diagnosed with Sarcoidosis in the department of Pulmonary Medicine.

Secondary:

Assess the extra-pulmonary manifestations of Sarcoidosis in the same Cohort of patients

Review of literature:

Sarcoidosis is a disease of unknown aetiology; it is known to produce non caseating granulomas in various organs. It is known to affect lung primarily, but can involve any organ in the body. Prevalence of sarcoidosis as mentioned in the epidemiology section of this study ranges from 0.03 to 640 per 1,00,000 depending on the sec, age and race(5). Common symptoms with which patients with Sarcoidosis present are that of pulmonary involvement with cough, breathlessness, but other nonspecific symptoms of sarcoidosis are fatigue, generalised weakness and loss of appetite and weight which don't directly correspond to the physical evidence available of the disease(11).

What is Fatigue??

Fatigue in common terms can be used for lethargy, excessive tiredness, and weakness. Fatigue is not only seen in many acute and chronic medical illnesses, but can also be seen in normal individuals in day to day life. It may hence be said that fatigue can be physiological, psychological or behavioural phenomena(12). Fatigue is one of the common symptoms patients might come out with once asked for, it rarely is the presenting symptom. Diseases other that Sarcoidosis which can cause fatigue may be related to the following:

A) Life-style habits: excessive alcohol intake, excessive physical activity, inactivity, lack of sleep, medications such as antihistamines, cough suppressants and unhealthy eating habits

B) Psychological conditions: Anxiety, Depression, Grief and stress.

C) Medical conditions: Sarcoidosis, Hypothyroidism, Hyperthyroidism, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Malignancy, Chronic fatigue syndrome, Chronic obstructive Pulmonary disease, Acute liver failure, Anaemia, Obesity, Obstructive sleep apnoea, Chronic kidney disease and medications like anti-depressants and anti-hypertensive.

Is Fatigue common in Sarcoidosis:

Fatigue is found to be very common among patients with Sarcoidosis. Fatigue is one of the most important symptoms affecting quality of life in patients with Sarcoidosis(13). Fatigue is defined as extreme tiredness due to physical, mental stress or illness. Fatigue is a symptom which is commonly neglected by patients and physicians. It has been seen that significant fatigue directly affects the quality of life of patients(14)(15) (16)(17)(18), hence affecting their socio-economic status. Fatigue is one of the most important extra-pulmonary manifestations of Sarcoidosis which is most often ignored in a clinical setting.

Prevalence of fatigue in Sarcoidosis:

Fatigue in Sarcoidosis is found to be higher compared to normal controls(19)(17). Fatigue was studied in many studies to identify the prevalence and burden in patients with Sarcoidosis. Different studies show variable prevalence ranging from 30 – 90%(20)(21) Sarcoidosis has been seen to present with fatigue in variable prevalence which may be because of the race as seen in a study done to compare the prevalence of fatigue in American and Dutch patients and found a higher prevalence of fatigue in American patients(22).

Sarcoidosis is thought to be an individual process and continues to progress irrespective of treatment of Sarcoidosis with drugs(23). There are only few Indian studies looking at the prevalence of fatigue which have the prevalence to vary from 30-70%, there are few reports from other places in India which have varied prevalence from 61.2-150 per 1,00,00 patients(10). Such high prevalence of Fatigue warrants urgent medical attention as it is seen as one of the most common extra-pulmonary manifestation.

How to objectively measure Fatigue in patients with Sarcoidosis??

We looked at various literatures to identify tools which have been used to assess fatigue in patients with Sarcoidosis.

Following are the tools which were identified:

- WHOQOL-100 (Mean 100 item World Health Organisation Quality of life questionnaire)(15):

Questionnaire comprises of 100 item dealing with physical health quality, social, spiritual and level of independence graded on a 5 point likert scale from 1(Never) to 5 (Always), it takes 15-20 minutes and is considered to be good in patients with Sarcoidosis.

- CRQ (Chronic Respiratory disease questionnaire)(24):

It consists of 20 items taking 20-30 minutes to fill, not considered to be appropriate for Sarcoidosis, but has been validated in interstitial lung disease

- SF-36 (36 item Short form Health survey)(24):

It is another health survey questionnaire which comprises of 36 items, takes about 10 minutes to complete and is considered to be good in assessing fatigue in patients with Sarcoidosis.

- SGRQ (St George's Respiratory Questionnaire)(15): Comprises of 76 items and consumes around 10-15 minutes. It is considered to be good for Sarcoidosis patients.

SHQ (Sarcoidosis Health Questionnaire): It is the only disease specific questionnaire comprising 29 items, takes about 10 minutes and is considered to be good in determining fatigue objectively.

- SIP (Sickness Impact Profile):

It comprises of 136 items and takes about 20-30 minutes and is credibility in Sarcoidosis is unknown

- DAL (Daily activity list) (25):

Deals with usual activities, consists of 11 items and is not found to be the best in Sarcoidosis but has been used in studies to assess Fatigue and health related quality of life.

- BFS (Borg Fatigue Score):

It is a rating scale for fatigue, similar to the Borg dyspnoea scale which is used. It ranges from 0 which means no fatigue at all to 10 which is maximum fatigue. It has neither been found to be reliable nor specific for fatigue in Sarcoidosis patients(26)

- CIS (Checklist individual strength):

A 20 item questionnaire dealing with severity of fatigue, concentration problems, decreased motivation and decreased physical activity(27)(28)(28)(28) It has been used in a study dealing with Sarcoidosis remission patients and fatigue(28), but has not been validated to be used for assessment.

- BDI (Beck depression inventory):

It is a 21 question multiple choice self-report inventory which has been used in some studies for measuring fatigue(29) , but is found to be more useful in assessing depression in chronic diseases

- FACIT-F (Functional assessment of chronic illness therapy - Fatigue):

This score uses 13 items dealing with fatigue for the last 7 days. It has been used in studies to assess improvement in fatigue after treatment(30)(31).

- Multi-dimensional fatigue inventory:

It is a 20 item measure of fatigue covering general fatigue, mental fatigue, physical fatigue, reduced activity and motivation(32). It has been used in patients with Sarcoidosis as well(33)(34)

- FAS (Fatigue assessment scale):

Most commonly used and validated questionnaire to assess fatigue in patients with Sarcoidosis is called as the Fatigue Assessment scale.(16)(29)(13)(33)(35)(30)(31)(36)(14). Since FAS has been validated for use in patients with Sarcoidosis, we used FAS in our study; it consists of 10 questions with a 5 point likert scale from never to always.

FATIGUE ASSESSMENT SCALE

	Never	Sometimes	Regularly	Often	Always
1. I am bothered by fatigue	1	2	3	4	5
2. I get tired very quickly	1	2	3	4	5
3. I don't do much during the day	1	2	3	4	5
4. I have enough energy for everyday life	1	2	3	4	5
5. Physically, I feel exhausted	1	2	3	4	5
6. I have problems to start things	1	2	3	4	5
7. I have problems to think clearly	1	2	3	4	5
8. I feel no desire to do anything	1	2	3	4	5
9. Mentally, I feel exhausted	1	2	3	4	5
10. When I am doing something, I can concentrate quite well	1	2	3	4	5

Why is FAS better than other Quality of life questionnaires?

FAS has 10 simple questions which can be answered in less than 15 minutes. It is found to be the most reliable and valid score which can be used for assessing fatigue in Sarcoidosis patients(13).

Reliability of FAS in Sarcoidosis is proven by the following reasons:

- Test - retest reliability is found to be good – 0.89, which is better than all the other scales mentioned above(29)(37)
- FAS' sensitivity to change is very good(29), hence it can be used in studies which deal with treatment of fatigue to measure objectively if significant change in fatigue is seen.
- Cronbach's alpha of FAS is also found to be good(38)(29)

With the above mentioned reasons, it can safely be said that FAS has high internal consistency in measuring fatigue.

Validity of FAS in sarcoidosis patients:

- Construct validity of FAS is good as it has questions pertaining to physical and mental health with 8 questions having no gender bias(29)(39)(33).
- Construct validity of FAS shows one underlying factor(38)(29).

- MCID of FAS which is a four point change is also found to be valid(40), this will be useful both in following up Sarcoidosis patients and in clinical trials.
- Discriminant validity of FAS is good and it has no floor or ceiling effects(38)

Therefore, Fatigue assessment scale is the most reliable and valid score to assess fatigue in patients in Sarcoidosis in both clinical trials like ours and in outdoor settings as well. A score of 22 or more in Fatigue is considered to be significant fatigue(41) (42)

Causes of fatigue in sarcoidosis:

Fatigue is common in Sarcoidosis as mentioned in the previous studies. Attempts to find the aetiology of fatigue in Sarcoidosis patients have been done. They found that the cause of fatigue is multifactorial(23)(13). Following are the causes identified for factors causing fatigue in Sarcodosis patients.

Increased inflammation and metabolic dysfunction

Increased inflammation results in granuloma formation and release of cytokines in Sarcoidosis which may lead to fatigue(13). TNF Alpha which is also called as cachectin and Interleukin 1 and 6 levels are found to be high (21) which contributes to fatigue.(43)

Myopathy – due to inflammation and/or drugs used to treat Sarcoidosis like steroids can cause myopathy(44)(16)(13). It can be part of the disease as an extra-pulmonary manifestation with muscle weakness(15). They can have either an acute polymyositis or a chronic myopathy, Chronic myopathy is more commonly associated with fatigue(45)

Pain – Arthralgia is one of the extra-pulmonary manifestations in Sarcoidosis and can lead to fatigue. Pain as part of the disease or due to neurological manifestations may present with fatigue(46)

Altered sleep patterns and/or associated sleep disorders are commonly seen in patients with Sarcoidosis and can induce fatigue (15). Sleep disorders like sleep apnoea, restless leg syndrome(47) have been found to more common in Sarcoidosis patients(48). A study states that patients with Sarcoidosis have 6-8 times increased prevalence of sleep disorder compared to normal population(49)

Psychological factors – significant number of patients with Sarcoidosis are seen to have anxiety and depression which mainly manifest as fatigue. These psychological factors seem to play a very crucial role in causing fatigue(50). Emotional stability in a study by Magnusson et all has been found to be the most important predictor of fatigue(51)(52)

Involvement of the Central nervous system can be seen in Sarcoidosis patients and fatigue is found to be more in them compared to others

Small fibre neuropathy – SFN is another common cause of fatigue and FAS scores are found to be higher in patients with SFN compared to non-Small fibre neuropathy Sarcoidosis patients(23)(46). It is a difficult condition to diagnose, but can be of use as TNF Alpha levels are found to higher in them and targeted therapy with Anti TNF Alpha drugs and immune globulins can be used(43)(50).

Few studies have shown patients with Sarcodosis to have a lower PiMax compared to normal individuals which may affect them and lead to fatigue(53)

It can thus be concluded that the exact cause of fatigue in patients with Sarcoidosis cannot be labelled to a single factor; multifactorial causation theory is the most accepted world-wide explanation for cause of fatigue in Sarcoidosis.

Types of Fatigue in Sarcoidosis:

Fatigue in Sarcoidosis has been classified into many types. Following are the available classification of fatigue:

Early morning fatigue, Intermittent fatigue and after noon fatigue. This classification is not a validated classification(54)

As study comparing the previous classification found the following results to be more valid for fatigue in Sarcoidosis

Mild fatigue: Patients with no or mild complaints of fatigue

Intermittent fatigue: Variable symptom of fatigue throughout the day

All day fatigue: Feeling fatigued for the whole

Above classification was approved by Kleijn et all and they advised psycho-social counselling for patients in the all-day fatigue group would be helpful as part of treatment(50).

Post Sarcoidosis chronic fatigue syndrome: This syndrome has been described in patients with Sarcoidosis after they are treated. They present with myalgia, malaise and depression

Treatment of fatigue in Sarcoidosis:

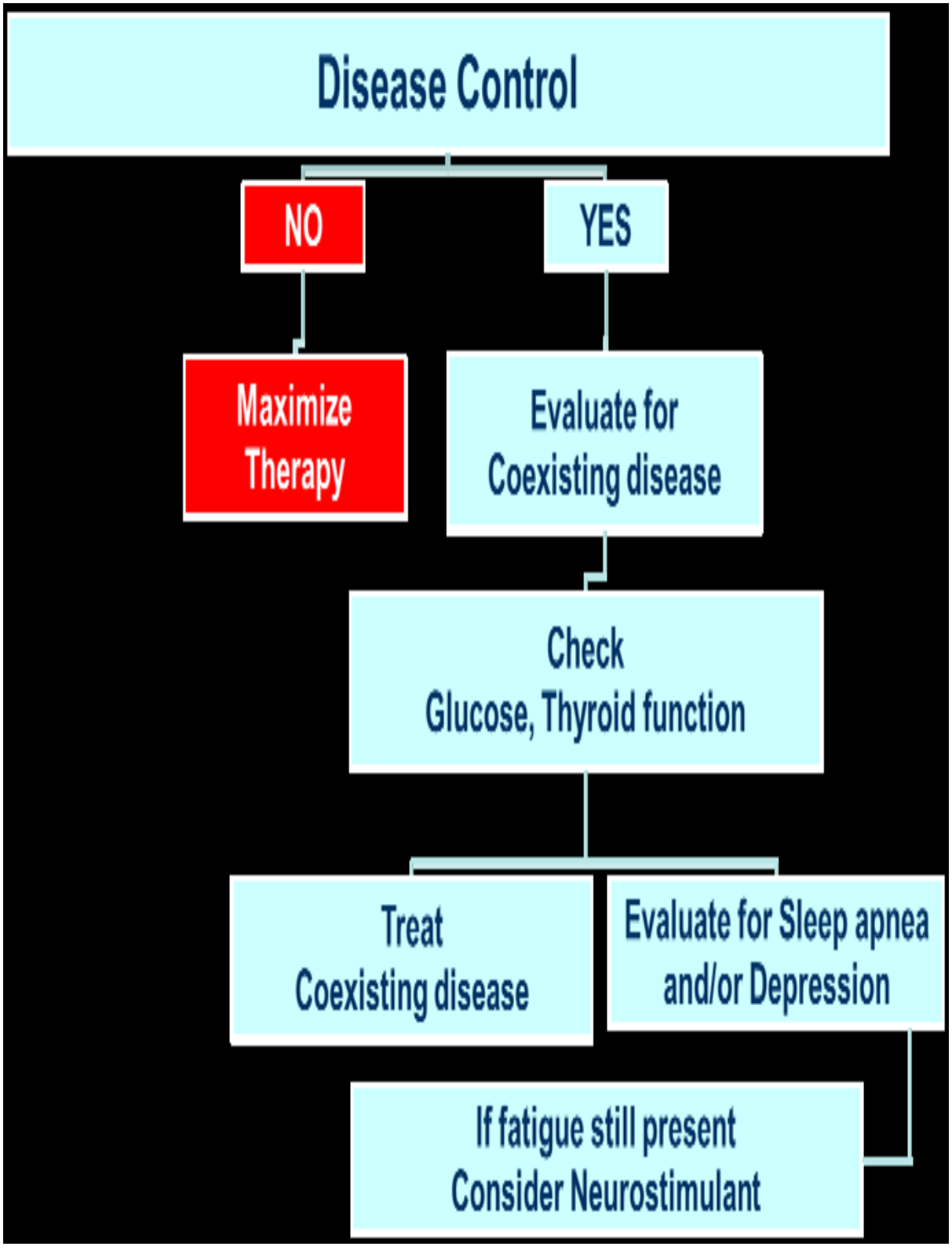
Fatigue is one of the most common presenting symptom which may be ignored in a clinical setting may lead to poor quality of life. This may affect the holistic care which a physician would like to offer to his/her patients with Sarcoidosis. Trials have been done with neurostimulants for the treatment of fatigue in Sarcoidosis. Following are the drugs which have been studied in Sarcoidosis patients to treat fatigue(30)(31)(53).

Methylphenidate/Dextro – Methylphenidate: In a cross over trial it was found that giving this drug improved fatigue with a MCID in FAS being 4.5. It was given for 4 weeks to obtain the MCID of 4.5(40)(31).

Armodafinil: Armodafinil is the r isomer of modafinil, both of which have been used to treat excessive somnolence. A cross-over study demonstrated improvement in fatigue in patients with sarcoidosis (30).

Anti TNF Alpha drugs: Anti TNF Alpha drugs like Infliximab and adalimumab have been studied in treating fatigue in Sarcoidosis with the hypothesis of reducing inflammation and reducing fatigue(37)(55)

Methylphenidate, D-Methylphenidate and Armodafinil are grouped together as neurostimulants. They are not to be given at the diagnosis of fatigue in Sarcoidosis. First step to treat fatigue in Sarcoidosis is by treating the cause i.e. by treating Sarcoidosis(56) . In addition to drugs cognitive behavioural therapy and rehabilitation programmes also help to reduce fatigue in patients with Sarcoidosis. Following is the most appropriate clinical approach which is to followed to treat patients with fatigue as per clinical trials


Disease Control
NO
YES
Maximize Therapy
Evaluate for Coexisting disease
Check Glucose, Thyroid function
Treat Coexisting disease
Evaluate for Sleep apnea and/or Depression
If fatigue still present Consider Neurostimulant

Maximising therapy for Sarcoidosis is the first step in managing fatigue, followed by treating co-existing disease like hypothyroidism, Diabetes mellitus and treating them appropriately. Evaluation of sleep apnoea with a polysomnography with or without depression needs to be identified and treated accordingly. If fatigue continues to be present after the above measures, neurostimulants like Methylphenidate, D-Methylphenidate and armodafinil can be considered.

EXTRA PULMONARY MANIFESTATIONS OF SARCOIDOSIS:

Sarcoidosis involves the lungs in 90% of patients but can involve virtually any organ or system in the body. Our secondary objective of the study was to look at the prevalence of extra-pulmonary manifestations in patients with Pulmonary Sarcoidosis who presented to our department. Some studies state that extra-pulmonary manifestations in Sarcoidosis can be as high of 50% to 65%(57)(58). Extra-pulmonary manifestations almost always present with concurrent Pulmonary involvement and is rarely seen alone. Following is the list of extra-pulmonary manifestations in decreasing order of prevalence:

1. Skin (15-25%),
2. Eye (10-15%),
3. Liver (10-15%),
4. Calcium(10-15%),
5. Spleen (5-10%),
6. Neurologic (2-5%),
7. Parotid/ Salivary gland (2-5%),
8. Bone marrow (2-5%),
9. ENT (3%),
10. Cardiac (2-3%),
11. Renal (0-1%),
12. Bones & Joints (0.5%) Muscle (0.4 %).

Recommended screening tests to identify extra-pulmonary manifestation of Sarcoidosis should include the following(58):

1. History (occupational and environmental exposure, symptoms)

2. Physical examination

3. Poster anterior chest x-ray

4. Pulmonary function tests: spirometry, DLCO

5. Peripheral blood counts: white blood cells, red blood cells, Platelets

6. Serum chemistries: calcium – serum and 24hr urinary levels, liver enzymes (alanine aminotransferase, aspartate aminotransferase, alkaline Phosphatase); creatinine, blood urea nitrogen

7. Urine analysis

8. Electrocardiogram

9. Routine ophthalmologic and dermatologic examination

Identifying and managing extra-pulmonary manifestations in Sarcoidosis patients is important in final outcome and prognosis of patients

Skin:

Naming of Sarcoidosis was based on skin lesions which were Sarcoma like.

Dermatological manifestation of Sarcoidosis is the most common extra-pulmonary manifestation of Sarcoidosis. They may present at any time of the illness, starting from presentation with a skin lesion instead of Pulmonary symptoms or late in the course of disease(59). In various up to 35% of dermatological manifestations were reported(60)(61)(62). Female preponderance for skin involvement has been reported(60). Not all skin lesions are specific for Sarcoidosis, only a tissue biopsy from the lesion showing non-caseating granuloma can be taken as significant proof of Sarcoidosis causing the lesion. Following is the list of cutaneous manifestations of Sarcoidosis:

Lupus pernio:

Affects the cheeks, nose, ears and lips, more common in women, more common above the age of 40(59). It is an indolent, red-purple, violaceous lesion. It is considered as one of the most specific lesions suggestive of Sarcoidosis(63).

Maculopapular lesion:

They are the most common manifestation in Sarcoidosis, they appear red-brown to purple, less than 1cm, presenting as an infiltrative lesion(59). Compared to Lupus pernio, prognosis of this type of manifestation is a favourable one.

Erythema nodosum:

Seen in around 10% of patients(6), they are elevated red round patches, which are painful, not specific for Sarcoidosis, it can be seen in other diseases but is a common manifestation of Sarcoidosis as well(59). Lofgren's syndrome as an acute presentation of Sarcoidosis with the triad of Erythema nodosum, Polyarthralgia and Hilar adeonopathy(64) with known association to HLA-DRB1*03.

Plaques:

They are round or oval in shape, ranging from millimetres to centimetres, another common manifestation of Sarcoidosis with a better prognosis(65)

Granuloma annularae:

Uncommon presentation, they are annular lesions and because of the granulomatous aetiology, called as Granuloma annularae.(59)

Psoriasiform lesions:

Scaly, follicular lesions like Psoriasis can be seen in Sarcoidosis, but It is important to rule out co-existing Psoriasis as they may present together(66)

Vitiligo: Autoimmune background of Sarcoidosis is well-known and can manifest as Vitiligo also due to its auto-immune nature(59).

Other skin lesions which can be seen in Sarcoidosis are Subcutaneous nodules, reactivation of an old scar tissue, foreign body manifestation(59)

Diagnosis and Treatment of Cutaneous Sarcoidosis:

Diagnosis is based upon the tissue obtained from the lesion showing non caseating granulomas. In all cases of cutaneous Sarcoidosis effort to identify systemic involvement should be done(59). A punch biopsy should not be attempted in a case of Erythema nodosum(67).

Treatment depends on the type of skin lesion and other factors like area of involvement and symptoms. Harmless skin lesions and those that do not cause disfiguration need not be treated(57).

Choice of therapy: Commonly used drugs in management of cutaneous Sarcoidosis are

Glucocorticoids – Local and Systemic

Antimalarial – Chloroquine and Hydroxychloroquine

Methotrexate

There are no studies to compare the efficacy of the aforementioned drugs in cutaneous Sarcoidosis. Local corticosteroids are impractical to use if the lesion is extensive (57). Systemic steroids can be administered in severe cases.

Lupus pernio, a variant of Sarcoidosis manifestation warrants treatment, since it is disfiguring, progressive and is associated with a poorer prognosis (57). TNF Alpha inhibitors like Infliximab have been used in Lupus Pernio(68)(69).

It can be thus concluded that Dermatological manifestations are very common among patients with Sarcoidosis, though it might not require treatment always when present. Only lesions which causes symptoms, disfigurement or can be associated with a poor prognosis needs to be treated. All patients with Dermatological manifestation as the presenting symptom, systemic Sarcoidosis should be looked for, since it rarely presents as a single organ involvement.

Ophthalmological manifestations:

After lung and Skin, the third organ to be affected in Sarcoidosis is the Eye. It is seen in about 25 -50% of patients with Pulmonary Sarcoidosis(70), a study states the prevalence of ocular manifestation being as high as 70% in Japanese(71). Ocular manifestation has been found to have variable prevalence in different races (69). In the western population More severe disease in seen in Blacks(69) and chronic or asymptomatic diseases are more commonly seen in Whites(72).

They may have varied presentation – They may be the first symptom patient presents with in Sarcoidosis, can present years before systemic manifestations(70). Following are the manifestations of Sarcoidosis in the Eye:

Uveitis – Anterior and Posterior(73)(71)(74):

Uveitis is the most common ophthalmological presentation in Sarcoidosis(6), anterior uveitis being more common than posterior uveitis. Anterior uveitis is usually granulomatous and has a chronic course compared to posterior uveitis(70). One of third of patients might be asymptomatic, but others present with Pain, redness, decreased visual acuity and photophobia which can be bothersome and might be the presenting symptom of Sarcoidosis.

Cystoid macular oedema(73)(71)(74):

Cystoid macular oedema usually results due to chronic uveitis. It is found to be refractory to the anti-inflammatory drugs which are used in Sarcoidosis and is vital in deciding the visual prognosis if present.(70)

Visual loss(73)(71)(74):

Visual loss may be the presenting symptom but is not specific for Sarcoidosis.

Conjunctival Nodules:

Conjunctival nodules are seen in up to 40% patients who have involvement of Eye(75)

Lacrimal gland swelling(73)(71)(74): Frequency of lacrimal gland being involved ranges from 7 to 69% and present with nasal stuffiness and epiphora(68).

Optic neuritis(73)(71)(74): Optic neuropathy is a relatively rare complication of Sarcoidosis. Patient presents with papilledema, papillitis and occasionally with granulomas on the optic head. There may be inadequate response to therapy and they develop optic atrophy. Systemic therapy may be required in patients with optic nerve involvement. Anti TNF Alpha blockers like Infliximab have to be used and have been found to be useful in treating patients who develop optic neuropathy.

Orbital disease:

Orbital disease is more commonly seen in elderly patients. It may involve the adnexa and the orbit. This leads to entrapment of the eye associated with diplopia.

Ocular biopsy demonstrating granuloma (73)(71)(74):

Occasionally only through an ocular biopsy is diagnostic of granulomatous invasion of eye by Sarcoidosis.

Miscellaneous manifestations: Patients with ocular Sarcoidosis in few case may present with Scleritis, Glaucoma or Cataract.

Diagnosis of Ocular Sarcoidosis:

Findings on an ocular examination suggestive of Ocular Sarcoidosis are the following:

- Mutton fat keratitic precipitates
- Iris nodules – koeppa / Bussaca
- Trabecular meshwork nodules
- Tent shaped peripheral anterior synechiae
- Snowballs, string of pearls vitreous opacities
- Multiple active or atrophic chorio-retinal peripheral lesions
- Nodular or segmental periphlebitis – “candle wax drippings”

- Optic disc nodules
- Retinal macroaneurysms

Definitive diagnosis of ocular Sarcoidosis would be an ocular biopsy but is not possible or required in all cases. ACCESS study used to define organ involvement in patients with Sarcoidosis lays down the following criteria:

Definition of Ocular Involvement in Patient with Biopsy-Confirmed Sarcoidosis(76)

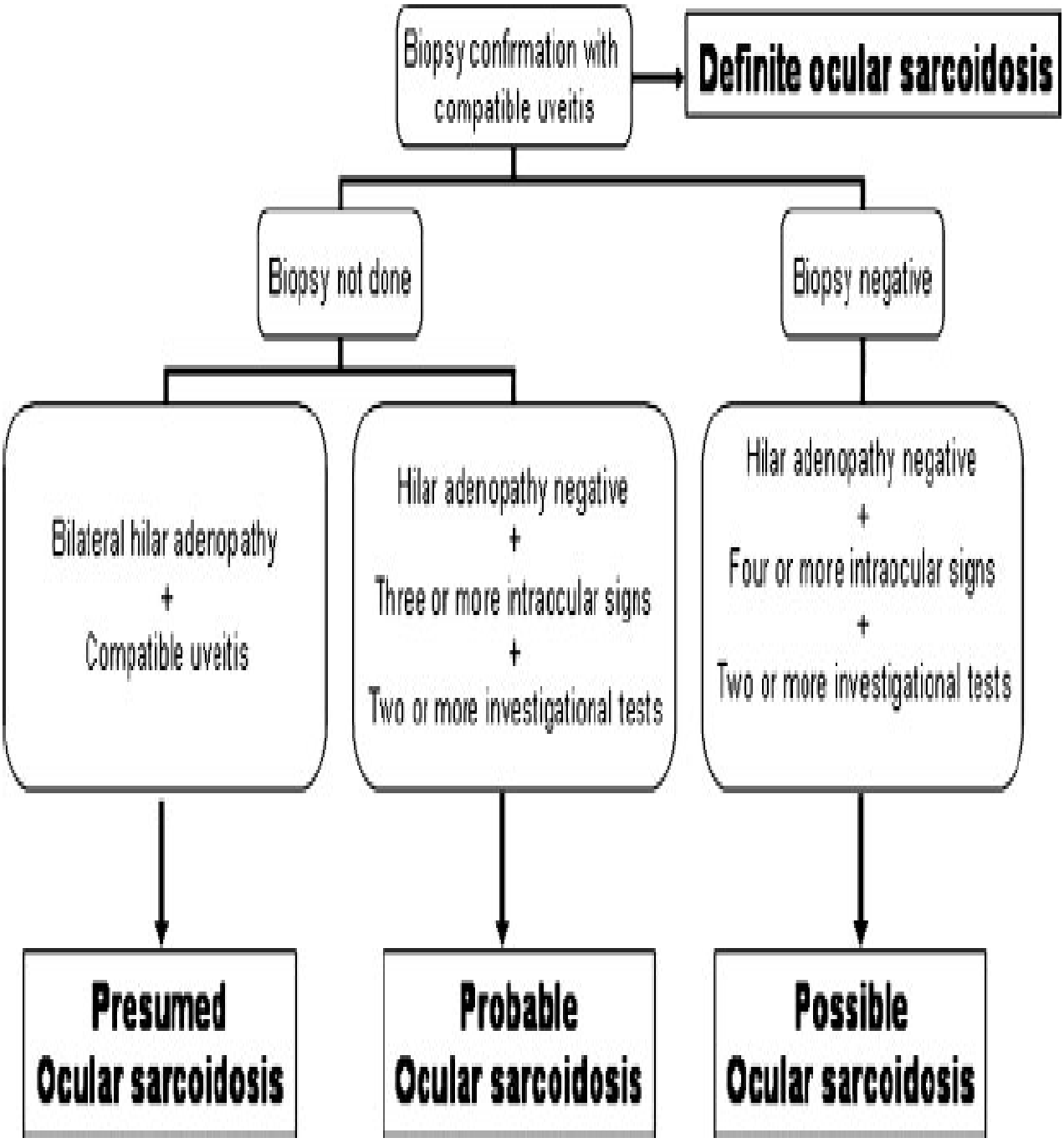
Definite ocular sarcoidosis

- Uveitis
- Lacrimal gland swelling
- Optic neuritis
- Ocular biopsy demonstrating
- Granulomas

Probable ocular sarcoidosis

- Blindness

International criteria used for diagnosing Sarcoidosis if biopsy is not possible is by the following Strategy(77):



Treatment of ocular Sarcoidosis:

A stepwise treatment of ocular Sarcoidosis is advised. It is advisable to start with topical steroids in patients with mild uvieitis, in most cases control can be achieved with that. In those control is still not possible or those who have a severe disease, topical and intra-ocular steroids can be used. If still control is desired, systemic corticosteroids are indicated. Other drugs which can be used are cytotoxic drugs like Methotrexate, Leflunomide, Azathioprine and Mycophenolate. When even with Steroids and Cytotoxic therapy control is not achieved TNF Alpha inhibitors like Infliximab can be used(72). There are studies on the human monoclonal antibody against TNF Alpha, Adalimumab in treating refractory cases of eye involvement even after treatment with infliximab(55).

Liver involvement:

Next organ to be involved as part of the extra-pulmonary spectrum of Sarcoidosis involvement is the Liver. Prevalence of liver involvement in Sarcoidosis also has a varied range. ACCESS trial looking at various organ involvement reported a prevalence of 11.6%(79). Some studies reveal a higher prevalence of liver involvement ranging from 50-90%(80)(5). Patients with liver involvement are usually asymptomatic and very few are progressive in nature. It is seen that 40-80% of patients, it is only a histological diagnosis, 25-35% will have abnormal liver function tests, 5-15% of them will present with symptoms like abdominal pain, hepatomegaly, pruritus, nausea, vomiting, weight loss and jaundice. Only a small percentage of them – 1% develop progressive and have serious consequences. But it is important to identify the presence of liver involvement at the time of diagnosis of Sarcoidosis. The most commonly missed finding is that of elevated liver enzymes.

Though most patients are asymptomatic and does not require treatment a small portion of the patients may present with one of the following:

- Chronic Cholestatic disease
- Portal Hypertension
- Cirrhosis

Sarcoidosis can affect the liver and present pathologically in the form of (81)

Cholestasis:

- Acute cholangitis
- Periductal fibrosis
- Ductopenia

It may present as a necro-inflammatory lesion with:

- Focal necrosis with mono nuclear infiltration

Fibrosis due to Sarcoidosis in liver presents as:

- Peri-portal
- bridging
- cirrhosis

Vascular changes seen are:

- Sinusoidal dilatation
- Granulomatous venulitis
- Nodular regenerative hyperplasia

Diagnosis of Liver Sarcoidosis not always warrants a biopsy from the liver. In a patient who has been diagnosed with Sarcoidosis has elevated liver enzymes i.e. alkaline phosphatase and Transaminases, or if the radiological finding is characteristic of Sarcoidosis in the liver, liver biopsy is not required to diagnose Sarcoidosis involvement of the liver. The most common radiological manifestation of Liver Sarcoidosis is Hepatomegaly(82). CT of the abdomen in some patients may reveal multiple low density intra-hepatic septa which are said to be characteristic presentation of Sarcoidosis (81). 5-19 % of patients are found to have focal nodules which are considered to be granulomas. These nodules characteristically range from 1-2cm , innumerable in number and are diffusely spread in the liver. These nodules do not have any peripheral enhancement (81). Sarcoidosis may involve the biliary tree as well where it mimics Primary biliary Cirrhosis closely and needs to be ruled out. The main differentiating feature is the absence of Ant mitochondrial antibodies (81).

Treatment of Liver Sarcoidosis:

Not all patients with Liver Sarcoidosis warrant therapy. Patients who have the following need to be treated:

- Symptoms or progressive organ damage
- Abnormal synthetic function

- Worsening Liver enzymes
- Abdominal pain, Jaundice with evidence of cholestasis

Other patients do not require treatment but a careful watch on Liver function tests with testing once in at least 3 months is recommended(5).

Therapy has been tried with the following:

- Corticosteroids
- Immunosuppressive
- Ursodeoxycholic acid
- Liver transplantation

Corticosteroids have been found to be useful in patients with Liver sarcoidosis, some studies have reported a mixed response and a drawback noticed is its inability to prevent Portal Hypertension(80), hence corticosteroids need to be given only when suspected organ failure is present (78).

Immunosuppresives like Azathioprine may in itself cause liver damage, so avoided in patients with Liver sarcoidosis. There are not sufficient reports on treatment of liver sarcoidosis with TNF Alpha inhibitors.

Ursode-oxycholic acid is the proven treatment for cholestatic disease. In all patients with suspected Cholestatic disease, Ursodeoxycholic acid should be prescribed. It has been shown to have significant improvement in liver function markers which are considered as a poor prognostic factor in patients with Liver sarcoidosis. (80)

Liver transplantation:

Liver transplantation is the definitive treatment in patients who have overt liver failure. (79) It should be reserved only for these patients as those who are on ursodeoxycholic acid or corticosteroids may still worsen and develop Cirrhosis.

Spleen:

Involvement of spleen by Sarcoidosis is seen in about 5-10 % of patients. Most common involvement of Sarcoidosis is in the form of Splenomegaly. 30-60% of cases are asymptomatic(83). Most common presentation like liver involvement is the presence of splenomegaly (84). It may be found in the clinical examination of the patients or in imaging of the abdomen. Massive splenomegaly is rare in patients with Sarcoidosis, but can be seen (82). All patients with splenic involvement don't have a poor prognosis and don't require treatment. Spleen involvement is most commonly seen in association with liver involvement. In some cases it can cause abdominal discomfort(85).

Most of them have good prognosis. A fine needle aspiration cytology may be obtained form the spleen in case of doubt of spleen involvement due to some other aetiology, which is rarely required as sarcoidosis presenting only with spleen involvement is rare. A cytology from the spleen is considered to be characteristic of Sarcoid involvement of spleen if it showed clusters of epitheliod cells (84).

Treatment in the form of splenectomy or corticosteroids is rarely required, it should be used only for patients with

Hypersplenism

Splenic rupture

Severe cytopenia

Prognosis of patients with Splenic sarcoidosis is good and most of the patients do not require treatment. Size of spleen has been seen to decrease variably.

Neurological manifestations:

Next common organ to be involved in Sarcoidosis is the Central nervous system, spinal cord and nerves. Prevalence of Neurosarcoidosis is around 5%(86)(87)(88). Some studies state a prevalence of up to 16%(89).

Neurological symptoms in a patient with Sarcoidosis can be due to any of the following

- Non Sarcoidosis disease
- It may be because of the granulomatous inflammation of the nervous system when it is called as Neuro-Sarcoidosis
- It can be because of Sarcoidosis but without causing granulomatous inflammation
- Patient may come with a neurological symptom because of the therapy or due to immunological alterations seen in Sarcoidosis.

Commonest Neurological symptoms with which Sarcoidosis patients present are:

- Headache
- Clumsiness
- Concentration problems
- Numbness
- Memory problems
- History of facial weakness

Most common manifestation of neuro-sarcoidosis is in the form of Cranial nerve palsy, facial nerve being the most common observed palsy(88).

Other manifestations of Sarcoidosis affecting the Nervous system may be myriad. Following is the list of range of neurological presentation when in an appropriate clinical setting, sarcoidosis should be considered as a possibility(88);

- Aseptic meningitis
- Encephalopathy
- Vasculopathy
- Mass lesions
- Seizures
- Hydro-cephalous
- Peripheral neuropathy
- Myopathy
- Myelopathy
- Hypothalamic – Pituitary disorders

Nervous system Sarcoidosis may present or leave a patient with High morbidity and hence an early suspicion and early diagnosis is always mandatory (88)(89). Severe forms of presentation are seen in acute stages of Sarcoidosis and Chronic Sarcoidosis usually present with peripheral nerve involvement and myopathy(86).

Diagnosis of Neuro-Sarcoidosis:

Diagnosis of neuro-Sarcoidosis requires tissue showing granulomatous inflammation. In 1999, a criteria was devised to diagnose Neuro-sarcoidosis to Definite, Probable and Possible as three criteria(90).

- Definite:

  Diagnosis based on Histo-pathology with a clinical picture of neuro-sarcoidosis and other disease has been ruled out.

- Probable:

  Clinical setting supports Sarcoidosis along with labarotory evidence of CNS inflammation due to Sarcoidosis i.e. elevated CSF Protein levels, oligoclonal bands, neurological evidence consistent with Sarcoidosis in imaging done (MRI) and systemic proof of Sarcoidosis in the form of positive histology from another site, positive Kveim's test, Indirect markers like high ACE levels, Gallium scans suggestive of Sarcoidosis and chest imaging in accordance with Sarcoidosis.

- Possible:

  When above criteria is not fulfilled but exclusion of other diseases have been done and clinical setting strongly suggests Neuro-sarcoidosis.

Radiological diagnosis:

MRI is the most relevant imaging modality used for Neurosarcoidosis. Following are the various presentations which can be appreciated in MRI in a case of Neuro-sarcoidosis(91):

- Dural meningeal Sarcoid
- Lepto-meningeal Sarcoid
- Enhancing brain parenchymal lesion
- Non-enhancing brain parenchymal lesions
- Spinal cord and nerve root involvement
- Cranial nerve involvement

Neurological manifestation may suggest prognosis of Sarcoidosis in them. It is important to characterise the type of lesion. It is seen that patients who have a cranial nerve lesion, a non-enhancing lesions or a Dura based lesion had better prognosis in comparison with spinal lesions, Brain parenchymal enhancing lesions or Lepto-meningeal involvement. MRI also proves to be good in follow up of patients showing significant resolution in lesions for patients those who respond to treatment(91).

Treatment of Neuro-Sarcoidosis:

Patients those who have been found to have Neuro-sarcoidosis in the central or peripheral nervous system and are symptomatic are always offered treatment considering significant mortality and morbidity.

Drugs which have been used in treatment of Neuro-Sarcoidosis are(90):

- Corticosteroids
- Infliximab
- Methotrexate
- Azathioprine
- Mycophenolate
- Cyclophosphamide
- Concomitant Anti-convulsant in patients with seizures

Drugs which have been shown to be beneficial only in case reports are(90):

- Chlorambucil
- Radiotherapy

It is advised to start cortico-steroids at higher dosage and then taper gradually. Studies show higher response rate with drugs like Cyclophosphamide and Methotrexate(92). Prognosis of neurosarcoidosis is found to be poorer compared with other extra-pulmonary manifestations due to its higher morbidity and mortality. Prognosis with peripheral nervous system involvement is better than those with central nervous system involvement(86).

Parotid/ salivary gland manifestation:

Parotid gland / salivary gland involvement in Sarcoidosis is seen in up to 6% of patients(93).

Following are the characteristics of parotid / salivary gland involvement in Sarcoidosis (93):

- Presents in the age group of 20-40 years
- More common in women
- 73% of them may present with bilateral disease

Most common symptom of involvement of these glands is an asymptomatic enlargement of both parotid glands. Other clinical presentations can be(94):

- Xerostomia
- Dysguesia
- Oral burning
- Xerophthalmia

Sicca syndrome can be associated with Sarcoidosis.

Heerfordt's syndrome:

When patients with Sarcoidosis present with uveitis, enlargement of the parotid glands and in some patients with facial nerve paralysis(95). Diagnosis of Heerfordt's syndrome also requires a histopathological diagnosis (95).

Diagnosis of parotid and salivary gland involvement will require a tissue from minor salivary glands showing non-caseating granulomatous inflammation(96). Gallium scan done is also found to be specific for patients who have minor salivary gland involvement. In patients who have biopsy proven non-caseating granulomas will have gallium uptake (96).

Bio-chemical studies done on the saliva from parotid gland of patients who have Sarcoidosis of the parotid show the following features(97):

- Decreased level of alpha amylase
- Increased albumin and Lysozyme

This suggests a pathological involvement if the gland due to inflammation leading to transfer of constituents from serum to saliva (97).

Panda sign:

Sign described on a radio-gallium scintigraphy when lacrimal, submandibular and Parotid glands are involved(98). This sign is found to be sensitive for Sarcoidosis.

Rarely parotid gland or minor gland involvement in Sarcoidosis requires treatment. Chronic sialadaenitis may develop in few patients in who surgical intervention might be required.

Bone marrow involvement:

Prevalence is around 5% in patients with Sarcoidosis

Diagnosis of bone marrow involvement in Sarcoidosis is always with the help of biopsy from the marrow demonstrating non-caseating granulomas (99) . Patients with Sarcoidosis involvement of the bone marrow may present with derangement of any of the cell lines(100):

- Anaemia
- Leucopoenia
- Lymphopenia

They found anaemia to be the most common presentation of Sarcoidosis affecting the bone marrow. Any patient in whom Sarcoidosis is suspected and has anaemia, leucopoenia or lymphopenia bone marrow biopsy has to be performed to rule out Sarcoidosis involvement of the marrow.

F-18 FDG PET / CT is found to have a higher sensitivity to identify Sarcoidosis involvement of the marrow(101)(102).

Treatment of patients with Sarcoidosis affecting the bone marrow is treatment with steroids which is used for systemic therapy(103). It has been seen that anaemia in patients which are due to Sarcoidosis reverse once treated with Sarcoidosis and might not require replacement. Work up of anaemia does not yield anaemia of chronic disease as seen in Tuberculosis.

ENT Manifestations:

Ear, nose and throat can also be involved in patients with Sarcoidosis.

Patients may be mistaken to have allergic rhinitis if a clinical suspicion of Sarcoidosis or other granulomatous diseases are not thought of since patients with Sarcoidosis affecting the Ear, Nose and Throat may present with(104)

- Rhinorrhoea
- Nasal obstruction
- Crusting
- Hearing loss

On examination findings which are non-specific for Sarcoidosis , but may be found are(105)

- Nasal polyps
- Erythematous Nodules
- Granulations on the turbinate
- Turbino-septal synechiae
- Septal deviation
- They may involve the maxillary sinuses along with nasal findings and present as Sino-nasal Sarcoidosis
- Nasopharynx involvement may be in the form of a pseudotumour

Gallium Scan may pick up involvement of sino-nasal sarcoidosis.

CT Done in them will have findings as noted in clinical examination of the patient with turbinate erosion, septal deviation and mucosal thickening of the sinuses when they are involved.

Good ENT examination and biopsy from the site will usually provide the diagnosis of sino-nasal Sarcoidosis.

Hearing loss in patients with Sarcoidosis may be because of involvement of the ear, but it may be due to central nervous system as well(106)(107).

Cardiac manifestations:

Next important organ which can be involved in Sarcoidosis is heart. Prevalence of cardiac involvement in Sarcoidosis is found to be about 5% (108). It is more commonly seen in Japanese and American population reaching up to 70-85% of cases(109). Common manifestations of cardiac sarcoidosis are(110):

- Ventricular arrhythmias
- Conduction blocks
- Pericardial effusion
- Congestive heart failure
- Pulmonary hypertension
- Ventricular aneurysm
- Sudden cardiac death
- Angina pectoris
- Valvular dysfunction

Cardiac involvement may be the presenting symptom in few cases, in most it either presents along with Lung involvement or just after diagnosis of pulmonary sarcoidosis.

Most case of Sarcoidosis affected hearts are found only during autopsy.(109).

In patients who has proven extra-cardiac sarcoidosis, in the event of patient developing cardiac failure or arrhythmias , cardiac involvement should always be considered(111). Patients who have dyspnoea which is not proportionate to the lung involvement should also be evaluated for cardiac sarcoidosis.

Pathologically cardiac sarcoidosis is seen to involve myocardium with autopsies demonstrating non caseating granulomas suggestive of sarcoidosis. Most patients were found to have myocardial involvement. Ventricles are more commonly found to be involved compared to atrium, but all chambers are involved.

Complete heart block in a young patient should always raise the suspicion of cardiac sarcoidosis in those patients.

They may clinically present as dilated cardiomyopathy as well.

Another rare presentation is the triad of congestive heart failure, malignant ventricular arrhythmia and high degree AV block (111), it needs to be differentiated from giant cell myocarditis before labelling as Cardiac sarcoidosis.

Diagnosis of cardiac sarcoidosis:

ECG is the first step in evaluating patients suspected to have cardiac sarcoidosis. Only 15% of patients who have cardiac sarcoidosis are found to have ECG changes at presentation. ECG changes also vary with severity of disease. More severe the disease earlier the ECG manifestation is observed(109). First step in diagnosis would be an ECG, if still strong clinical suspicion persists, next step in evaluating a patient of cardiac sarcoidosis is with Holter monitoring and 2D Echocardiography is must. Echocardiography may reveal a low ejection fraction suggestive of cardiac failure. 2D Echocardiography being a cheaper and non-invasive investigation had been commonly used in diagnosis of patients with Sarcoidosis. Sensitivity of Echocardiography can be increased by doing a stress echocardiography as well.

Next step in evaluating a patient with cardiac sarcoidosis is Radiological investigations which includes CT, MRI or Gallium scan.

CT is not the recommended mode of modality in imaging the heart, myocardial thinning may be the only feature seen in CT(112).

MRI is the modality of choice. Following are the findings which can be seen in Cardiac sarcoidosis (112):

- Trans mural or mid-wall delayed enhancement
- Nodular hyper intense foci on t2 weighted imaging
- Areas of myocardium may be found to be thickened

Other modalities which are used are the thallium and gallium scans. It should be reserved for only patients who have cardiac symptoms and a high clinical suspicion of Sarcoidosis is present.

Invasive diagnostic procedures:

Cardiac catheterisation to look for co-existent coronary artery disease can be done.

End myocardial biopsy which was started in 1962, the biopsy is usually obtained from the right ventricle, though left ventricle is found to have the most common involvement. Sample being non representative is a possibility in such a setting(109).

To diagnose a patient with Cardiac sarcoidosis, requirements would be to obtain histological proof of non-caseating granulomas along with one of the clinical and/or radiological features mentioned above.

Management:

As with other organ involvement, corticosteroids remain the mainstay of treatment. There can be a higher rate of mortality if patients are not carefully monitored and observed. Corticosteroids have been found to have a good prognosis in patients with Cardiac sarcoidosis if treated early.

Anti-arrhythmics may be required in patients who present with arrhythmia. Occasionally an in situ automatic implantable cardioverter defibrillator might have to be placed, the decision to place one of those is patient based and might not be warranted in those who revert with medical management.

Immunosuppressive agents have been tried in cardiac sarcoidosis. Following are the drugs which have been used:

- Methotrexate
- Azathioprine
- Cycloserine
- Thalidomide
- Pentoxifylline
- Infliximab
- Hydroxy-chloroquine

Some people have combined an immune-suppressant to corticosteroids to decrease the dose of long term steroids.(109).

Other options available for patients with Cardiac sarcoidosis are Heart transplantation. It is recommended for only those who have severe and recurrent heart failure and do not

respond to conventional medical therapy (109). Sarcoidosis in the heart transplanted is also a possibility, but can be treated sufficiently with Steroids.

Prognosis of Cardiac sarcoidosis is not very well defined and it depends on early diagnosis and treatment.

Patients who are started on cortico-steroids are found to have survival rate of 75% in a 5 year follow up study.

Bone / Joint and Muscle involvement:

Patients with Pulmonary sarcoidosis can have involvement of Bone/Joint and Muscle involvement. It is found to be low at the initial presentation 1% and gradually the prevalence of bone, joint and muscle involvement may go up to 13%(113). Osteo-articular manifestations may or may not be specific to Sarcoidosis.

Following are the Rheumatologic manifestations seen in patients with Sarcoidosis:

Acute Sarcoid arthritis

Chronic Sarcoid arthritis

Sarcoid synovial and tendinous involvement

Asymptomatic muscle involvement has been observed in 25-75% of patients.(114)

Acute polymyositis like syndrome

Tumorous sarcoidosis of the Muscles

Chronic progressive myopathy

Bones – hands are the most commonly affected structures(115)

Lace like pattern may be seen

Sclerotic bone lesions

Osteopenia / osteoporosis

Significant skeletal muscle weakness has been seen in patients with Sarcoidosis(45) which may contribute to fatigue in these patients.

Diagnosis of musculoskeletal involvement is done with the help of history suggestive of the same along with tissue diagnosis of non caseating granuloma in a biopsy specimen.

Treatment of patients with musculo-skeletal involvement in Sarcoidosis is according to the symptomatology of the patients. Those who have mild arthritis can be managed with NSAIDs and cold packs(113). Systemic cortico-steroids are also found to be effective. There are studies stating colchicine as another option in treating these patients.

Prognosis of joint involvement in Sarcoidosis is considered to be good with recovery seen in 1-6 months depending on the severity of the disease.

Patients who have a chronic destructive synovitis may need intraarticular steroids.

Patients with bone involvement have been seen to have a poorer prognosis, with the lesions being unresponsive to therapy

Calcium / Renal manifestations:

Calcium metabolism is found to be deranged in patients with Sarcoidosis.

Prevalence of calcium derangements in serum or urine in patients with Sarcoidosis varies from 5-50% (116).

Patients with these derangements may present with one of the following:

Hypercalcemia

Hypercalciuria

Decreased bone density

Increased serum concentration 1,25 dihydroxy cholecalciferol(117)

Very few case reports may be found where patients do not have Lung involvement but present only with calcium metabolism derangement.(118)

Following are the pathogenesis of Sarcoidosis affecting calcium metabolism:

Extra-renal synthesis of calcitriol causing derangement in calcium homeostasis

Alteration in activity of PTH – Parathormone

PTH related peptide expression

Clinically hypercalciuria is seen in up to 62% of patients with Sarcoidosis. Hypercalcemia to cause significant symptoms is not commonly seen.

Nephrocalcinosis due to long standing hypercalciuria may be seen in some patients

Some of them may present with Nephrolithiasis, renal failure which is seen to be rare in patients with Sarcoidosis.

Investigations which are required when evaluating a patient with suspected renal involvement due to Sarcoidosis are :

- Serum Calcium and albumin
- 24 hour urinary collection for calcium > 400 considered to be significant
- Creatinine to assess the functional status of the kidneys
- Ultrasonography of the abdomen to look for Nephrolithiasis and Nephrocalcinosis

Management:

Patients started on steroids seem to show good improvement except for bone mineral density which might be reduces further.

There are reports of thiazide diuretic used in management on hypercalcuria, but has not been accepted worldwide.

Surgical intervention for nephrolithiasis should be continued as per indications for any other aetiology.

Their prognosis is not considered to be poor if treated adequately

Methodology:

Sarcoidosis is a multi-system disorder, mainly involving the lungs. Other organ involvement is as mentioned in the previous section on review of literature. This study was designed to assess the importance of fatigue in patients diagnosed with Pulmonary Sarcoidosis. It was also designed to assess the prevalence of other extra-pulmonary involvement. Aims and objectives of the study are mentioned below

Aim –

Assessment of fatigue and other extra-pulmonary manifestations in patients diagnosed with Pulmonary Sarcoidosis

Objectives –

Primary:

Prevalence of Fatigue in all patients diagnosed with Sarcoidosis in the department of Pulmonary Medicine.

Secondary:

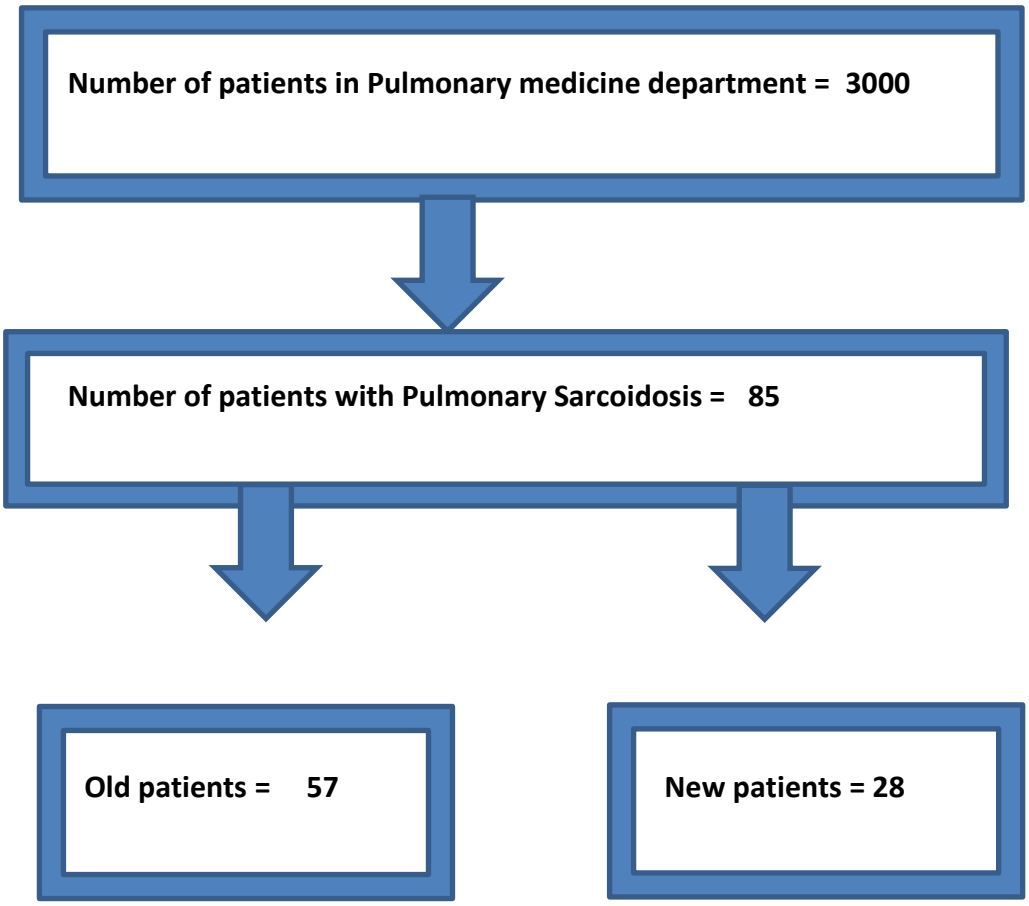
Assess the extra-pulmonary manifestations of Sarcoidosis in the same Cohort of patients

We planned to include all patients who are diagnosed with Pulmonary Sarcoidosis to be included in the study. Plan was to calculate the prevalence of Fatigue in all patients diagnosed with Pulmonary sarcoidosis. To calculate the same, literature of review done prior to inception of the study revealed an approximate prevalence of 50-70% in previous studies of same nature. With help of a statistician, sample size was calculated which is given as follows:

Single Proportion - Absolute Precision			
Expected Proportion	0.5	0.5	0.5
Precision (%)	10	15	17.5
Desired confidence level (1- alpha) %	95	95	95
Required sample size	96	43	31

To obtain a minimum of 43 patients to get results with a precision of 15% was planned. To get the required number of patients it was estimated that approximately 1500 patients need to be screened to diagnose around 40 patients with Sarcoidosis. We decided to include as many patients as possible during the period of January 2014 to August 2014. We managed to include 75 patients into the study.

STROBE Figure showing the flow of patients into the study:



As mentioned above we included 75 patients with Pulmonary Sarcoidosis out of which - 28 Were new patients and 57 were old patients. We decided to include patients with histopathologically proven Sarcoidosis from the age group of 15 to 100 Patients who were seen in outpatient or patients who were admitted were also included. They were included irrespective of their treatment status. Both treatment naïve and Patients who were on treatment were included with careful documentation of their treatment status.

A pulmonary histopathological diagnosis was not always necessary, diagnosis from biopsy of any other organ (e.g. Skin, Liver, Bone marrow) along with clinical and radiological relevant pulmonary features were considered sufficient.

Summarising the inclusion criteria:

Inclusion criteria:

All patients with diagnosed Sarcoidosis, clinically and biopsy proven (both treatment naïve and on treatment) , as outpatient and inpatient in the department of Pulmonary Medicine in CMC Vellore from the period of January 2014 to August 2014.

Since the primary objective of the study was to look at the prevalence of fatigue, After review of literature as mentioned in the previous section, we designed the Exclusion criteria to avoid confounding.

Exclusion criteria:

1.Anaemia(Haemoglobin levels of less than 10gm% in males and 8gm% in females) – Since anemia has been to shown to cause a certain level of fatigue, to avoid confounding, all patient who had anemia with the above mentioned levels were excluded from analysis.

2. Hypothyroidism :-

Hypothyroidism can present with fatigue being a common symptom, it was decided that patients who do not have hypothyroidism were Included for the study, or patients who have been diagnosed with hypothyroidism
but are on replacement with TSH levels being less than 8 were included, other had to be excluded to avoid confounding.

3. Existing malignancy (diagnosed and/or on treatment) :-

Malignancy has been a proven cause of fatigue and was hence considered exclusion criteria to avoid confounding. All patients who have a diagnosis of malignancy at the time of inclusion into study were excluded for assessment of fatigue.
Even patients who were on treatment for any malignancy were excluded for the same reason.

4.Tuberculosis :-

Tuberculosis of any organ is known to manifest with fatigue which
Can act as a confounding factor in our study hence all patients with Tuberculosis, or Patients who had concurrent tuberculosis, or patients who were labelled as probable Sarcoidosis due to doubtful co-existing tuberculosis, and/or were put on both Anti- tuberculous therapy and treatment for Sarcoidosis were also excluded for the same reason.

After making sure that a patient does not meet any exclusion criteria, study done was explained to him/her, an informed consent was obtained; once they consented for taking part in the study, for details view annexure. Once they gave consent, demographic details including their name, age, sex, profession, marital status were noted. They were asked to fill in a questionnaire on fatigue known as ' Fatigue assessment scale' this is a validated measure for fatigue in patients with sarcoidosis. The questionnaire comprises of 10 questions dealing addressing various aspects of both physical and mental fatigue, with the options of 1-5 in each.
Adequate time was given to each patient and the questionnaire administered was in the language which the patient is fluent in. Total score was calculated
once the patient completed the questionnaire. A score of 22 or more was considered significant to indicate significant fatigue. Details including the time since diagnosis and detailed treatment history was recorded. The prevalence of fatigue was thus calculated.

Secondary objective of the study was to assess the prevalence of other extra-pulmonary manifestations in the same cohort of patients.

The commonest organ to be involved in Sarcoidosis is the lung. The other organs in Decreasing order of prevalence as per literature is as follows:

1. Skin
2. Eye
3. Liver
4. Spleen
5. Brain
6. Parotid/Salivary gland
7. Bone marrow
8. ENT
9. Heart
10. Bone, Joint, Muscle
11. Kidney

12. Hypercalcemia / Hypercalciuria

Commonest extra-pulmonary organ involvement being Skin and Eye, arrangements were Made for all patients to be screened by a senior dermatologist and a senior Ophthalmologist. Patients who already had documented Skin or eye involvement were not subjected to repeat examination unless the present condition required review. For 5 patients Dermatological and Ophthalmogical screening could not be done due to personal inconveniences.

Since other organ involvement was less common, basic screening tests included, system specific history and physical examination, an ECG was done to look for rhythm abnormalities - arrhythmias or heart blocks-, peripheral blood counts (WBC, Hb, Platelets) were done to look for bone marrow involvement, Serum and urinary Calcium levels were obtained for abnormalities in calcium metabolism, Liver function tests were done to look for liver involvement (Liver enzymes more than thrice the normal will be considered as abnormal), an ultrasound abdomen was not routinely done, but performed if the liver function tests were abnormal. Urine-analysis, serum creatinine & Urea were done to look for renal involvement. Any abnormality found in any of the screening tests, were followed up with more detailed investigations as required or referral to concerned speciality department for

expert opinion. The prevalence of extra-pulmonary manifestations were finally collated in these patients. (Performa for extra pulmonary sarcoidosis is appended in the annexure)

RESULTS:

All 75 patients recruited had pulmonary sarcoidosis, which was histo-pathologically proven. None of them met any of the exclusion criteria mentioned in the methods section. The primary and secondary objectives were assessed in this group

BASELINE CHARACTERISTICS:

Baseline Characteristics of the patients are given below in Table 1. We included 75 patients into the study. Mean age of the patients were 47.27 with a standard deviation of 10.2. As shown in table 2, maximum number of patients (32,47%) were in the age group of 40-49. There were more male patients than female patients, although in published literature, the disorder is described to be slightly more common in females. Since many patients travel long distances to get evaluated at CMC, part of the reason for this skew may be referral bias. This was a bidirectional study and included patients who were newly diagnosed as Pulmonary sarcoidosis and also those on follow up, who were on treatment or on post treatment follow up. The number of new patients included in the study was - 28 and other diagnosed previously were 47, 37 of whom were on steroid treatment. Radiological staging of Sarcoidosis was done on all the patients, we had maximum number of patients in Stage 2 (45 , 60%).

Table 1 Baseline characteristics	
Age	47.27 (10.2)
Sex	
Male	41 (54.7)
Female	34 (45.3)
Diagnosis Status	
New	28 (37.3)
Follow up	47 (62.7)
Marital Status	
Married	3 (4)
Unmarried	72 (96)
Staging	
Stage 1	10 (13.3)
Stage 2	45 (60)
Stage 3	16 (21.3)
Stage 4	4 (5.3)
Steroids	
Yes	37 (49.3)
No	38 (51.7)

Table 1: Table showing baseline characteristics of patients with Pulmonary Sarcoidosis included in the study. The standard deviation for age and percentage for other variables are within parenthesis.

Table 2 showing age distribution of the patients

Age	Frequency (No / Percentage)
< 40 yrs	12 (16)
40 - 49 yrs	32 (42.7)
50 - 59 yrs	22 (29.3)
60+ yrs	9 (12)

Table 3 showing distribution of dose of steroids in patients on treatment, the doses are presented as Prednisolone equivalent

Dose	No / Percentage
>40mg	0 (0)
20-39mg	3 (8)
11-19mg	12 (32.4)
0-10mg	22 (59.4)
Total	37

Table 4 shows duration of steroid treatment in months

Duration	No (%)
< 6 months	4 (10.8)
6-12 months	7 (18.9)
>12 months	26 (70.3)
Total	37

Table 3 and 4 deal with the dose and duration of steroids. Steroids due to their effect in causing myopathy can lead to fatigue and hence details of the duration and dose of steroids were captured to analyze if statistically significant association is found and whether it can be a confounder. . Fifty nine percent of the patients were on less than 10mg of steroids and 70% of the follow up patients had been on treatment for more than a year.

PREVALENCE OF FATIGUE:

A total of of 55 subjects(73%) were detected to have fatigue on the basis of the fatigue questionnaire.

Table 5 shows the prevalence of fatigue in new vs. old patients

	FAS >21	FAS ≤ 21
New	24 (85.7%)	4(14.3%)
Old	31 (66%)	16 (34%)
Total	55 (73%)	20 (27%)

As is evident from Table 5, patients who were newly diagnosed and had not received any treatment, had a higher prevalence of fatigue 85% VS 66% in those who were on treatment and or on follow up.

Age also may seem to play an important role in fatigue, with the elderly expected to have more fatigue compared to younger group of patients. We looked at prevalence of fatigue in the various age groups, and we did not find any obvious difference (Table 6)

Table 6 Prevalence of Fatigue in different age groups

Age	FAS > 21	FAS ≤ 21
< 40 yrs	10 (83.3%)	2 (16.7%)
40-49yrs	24 (75%)	8 (25%)
50-59yrs	14 (63%)	8 (36.4%)
>60 yrs	7 (77.8%)	2 (22.2%)

We also looked to see if there is any difference in the prevalence of fatigue between males and females. Our results are displayed in Table 7 as follows:

Table 7 Prevalence of fatigue based on gender

	FAS > 21	FAS ≤ 21
Male	29 (70.7%)	12 (29.3%)
Female	26 (76.5%)	8(23.5%)

We found that female gender had slightly more prevalence in Fatigue compared to male gender 76.7% vs 70.7%, but it was not found to be statistically significant.

We also looked at patients who were on steroids and the prevalence of fatigue in them. It is shown in Table 8.

Patients who were on treatment were found to have a lower prevalence of fatigue compared to patients who were not on treatment.

On treatment	FAS > 21	FAS ≤ 21
Yes	25 (67.6%)	12 (32.4%)
No	30 (80.9%)	8 (21.1%)

Table 8 Prevalence of fatigue based on steroid treatment

Table 9 shows the prevalence of fatigue in sarcoidosis patients who were being treated with steroids

Steroids	FAS > 21	FAS ≤ 21
Yes	25 (67.6%)	12 (32.4%)
No	6 (60%)	4 (40%)

There was no significant difference in the level of fatigue in patients between those who were on steroids and those who were not on steroids.

Analysis was done to look at the prevalence of fatigue in relation to duration of sarcoidosis since diagnosis. Following is a table which shows the prevalence according to their duration since diagnosis in old patients.

Table 10 showing prevalence of fatigue in patients against duration since diagnosis of Sarcoidosis

Duration	FAS > 21	FAS ≤ 21
0-1 Month	23 (85.2%)	4 (14.8%)
1-6 months	3 (75%)	1 (25%)
6-12 months	5 (71.4%)	2(28.6%)
>12 months	24 (64.9%)	13 (35.1%)

As the duration since diagnosis increased, the fatigue decreased.. In patients who are just diagnosed in their first month the prevalence is 85.2% and as the duration crosses 1 year the prevalence in that group of patients is only 64.9%. Although we did not find any statistical significance using the chi square test, we found a p value of 0.346

Extra-pulmonary manifestations are common in Sarcoidosis and the prevalence of fatigue in those with other extra-pulmonary manifestation was also studied. We looked at various extra-pulmonary manifestations and if any particular extra-pulmonary manifestation had more prevalence of fatigue compared to others. Following is a table which depicts the same.

Table 11 showing Extra-pulmonary manifestation of Sarcoidosis and prevalence of fatigue in each group

Extra-pulmonary manifestation	Prevalence of fatigue
Skin	73.3
Eye	70
Liver	70
Spleen	85.7
Brain	66.7
Parotid gland	100
Bone, Joint, Muscle	73
ENT	33
Cardiac	100
Calcium/renal	80

There was only one patient each with parotid and cardiac manifestations and both of them had fatigue. Overall, there was high prevalence of fatigue in those with extra pulmonary symptoms.

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We did logistic regression and calculated the odds of fatigue in variables such as presence of significant fatigue and whether age, sex and use of steroids were risk factors for development of fatigue. Following is the table showing results from that:

Table 12 Correlation of fatigue with various risk factors :

Variable	odds ratio(CI 95%)	p value
Steroids	0.98(0.96-1.0)	0.752
Age	0.99(0.98-1.0)	0.084
Female sex	1.09(0.83-1.4)	0.478

However, presumably because of the small numbers, this did not reach statistical significance.

SECONDARY OBJECTIVE: EXTRA-PULMONARY MANIFESTATION

Secondary objective of our study was to present the prevalence of Extra-pulmonary manifestations in the same cohort.

Table 13 showing prevalence of various extra-pulmonary manifestations in Sarcoidosis Patients

Extra-Pulmonary Manifestation	Prevalence (%)
1.Skin	20%
2. Eye	26.6%
3. Liver	13%
4. Spleen	9.3%
5. Brain	4%
6. Parotid gland	1.3%
7. ENT	4%
8. Heart	1.3%
9. Bone/Joint/Muscle	10.6%
10. Calcium/ Kidney	6.6%

We found that 45 out of the 75 patients had extra-pulmonary involvement of some organ. This suggests that up to 60% of patients may have extra-pulmonary manifestation, if carefully looked for. Since eye and skin are the most commonly involved organs in sarcoidosis, screening by specialists was done to identify presence of eye and skin manifestation. We found a high prevalence of ophthalmological and dermatological manifestation, 26.6% and 20% respectively. Next extra-pulmonary organ involvement was that of the liver – 13 % of patients had liver involvement, followed by bone, joint and muscle involvement in 10% of patients.

Table 14 The frequency of extra-pulmonary involvement:

No of EP	Frequency
0	30 (40%)
1	25 (33.3%)
2	14 (18.7)
3	5 (6.7%)
4	0 (0)
5	1 (1.3%)

Table 14 shows that patients can have up to 5 extra-pulmonary involvements simultaneously. 6.7% of them having 3 extra-pulmonary organ involvements.

Around 18% of patients had 2 organs other than lungs involved due to Sarcoidosis. This data might be slightly skewed towards the higher limit as the study was performed in a tertiary referral centre, but definitely it reiterates the need to careful look out for extra-pulmonary manifestations in patients presenting with Sarcoidosis.

Each organ has its characteristic manifestation in Sarcoidosis, our next section of results deals with each extra-pulmonary organ and respective prevalence of each type of manifestation in the sub group.

Skin:

Dermatological manifestations may vary from a non-specific lesion like erythema nodosum to a specific disfiguring lesion like Lupus pernio.

Table 15 showing various Dermatological manifestations in Sarcoidosis patients

Skin manifestation	Prevalence
Lupus pernio	2 (13.3%)
Maculo papular	9 (60%)
Annular lesions	1 (6.7%)
Erythema nodosum	3(20%)

There were 15 patients with Dermatological manifestation, out of which the most frequently encountered was maculo-papular lesions – 60%, followed by Erythema nodosum

and Lupus pernio and annular lesions in that order. We found relatively more maculo-papular lesions compared to lupus pernio as described in the literature(67).

EYE:

Next most common organ to be involved as per literature is the eye. But we found a higher prevalence of ophthalmological involvement than Dermatological manifestations. 20 out of the 75 patients had involvement of the eye. Eighty percent of the patients presenting with uveitis and the rest with kerato-conjunctivitis. We did not find other involvements of eye like cystoid macular edema.

Table 16 Prevalence of Ophthalmological manifestation in Sarcoidosis patients

Eye	Prevalence
Uveitis	17 (85%)
Kerato-conjunctivitis	3 (15%)

LIVER:

Next most commonly involved organ was liver. We found 10 among 75 patients who had liver manifestation. There was equal prevalence of elevated liver enzymes i.e. transaminases and alkaline phosphatases and hepatomegaly. There were 2 patients who had proved liver involvement with histopathology showing granulomatous inflammation.

Table 17 showed liver involvement in Sarcoidosis patients

Liver	Prevalence
Elevated enzymes	4 (40%)
Hepatomegaly	4 (40%)
Liver granuloma	2 (20%)

SPLEEN:

Splenic involvement was seen in 7 out of 75 patients. All of them had splenomegaly as their manifestation and did not have any other spleen involvement.

NERVOUS SYSTEM:

Nervous system involvement can lead a higher morbidity compared to other extra-pulmonary manifestations and hence their identification is important. We found 3 patients out of 75 to have cranial nerve palsy. We did not find any other manifestation of neuro-sarcoidosis in our patients.

PAROTID AND SALIVARY GLAND:

Parotid and Salivary gland involvement is another commonly reported involvement in Sarcoidosis, but we did not find that to be true in our population. We had only one patient who had parotid involvement in the form of Parotitis.

ENT:

Ear, Nose and Throat can also be involved in patients with Sarcoidosis. Commonest manifestation we found was hearing loss which can be attributable to Sarcoidosis. It was seen in 3 patients out of 75. We did not find any other manifestation of ear, nose or throat.

HEART:

Cardiac manifestations can also be seen in Sarcoidosis and it is most commonly found in Japanese population. We found only 1 patient to have Cardiac involvement in the form of conduction block. We did not have patients with any other manifestations.

BONE / MUSCLE / JOINT:

Involvement of bone, muscle and joint can be in the form of arthritis, arthralgia, myopathy. We found prevalence of this to be high with 8 out of 75 patients having Bone, Muscle and Joint involvement.

Most of the patients had arthralgia as their primary manifestation. Interestingly, few of these patients presented in the Rheumatology department with arthralgia as their primary symptom.

Table 18 Prevalence of Bone/ Joint/Muscle involvement in Sarcoidosis patients

Bone/Joint/Muscle	Prevalence
Arthralgia	7 (87.5%)
Arthritis	1 (12.5%)
Others	0

KIDNEY / CALCIUM (HYPERCALCEMIA, HYPERCALCIURIA):

Patients may have involvement of the kidneys even present with renal failure. There were none with renal failure in our cohort. Hypercalciuria and Hypercalcemia which was seen to be 2 and 3 respectively in our cohort of Sarcoidosis patients.

Table 19 showing prevalence of Calcium / Renal involvement in Sarcoidosis patients.

Calcium / Renal	Prevalence
Hypercalcemia	3 (60%)
Hypercalciuria	2 (40%)
Others	0

DISCUSSION:

Pulmonary Sarcoidosis is a multi-system, granulomatous disorder affecting the lung most commonly, followed by other organs like Skin, Eye, Liver, and Brain. Sarcoidosis can virtually affect any organ. It is diagnosed on the basis of a concordant clinical picture, radiological correlation and histo-pathological diagnosis.

Our aim was to look at a symptom which is usually neglected in clinical practice. Fatigue synonymously used with excessive tiredness, malaise, lethargy and depression is one of the common symptoms which a patient experiences when he suffers with Sarcoidosis. This symptom is neglected and when not addressed leads to poor quality of life in patients. There have been only few trials looking at the prevalence on fatigue in patients with Sarcoidosis. There is no approved treatment for fatigue in patients who suffer with Sarcoidosis. Drugs which fall into the category of neuro-stimulants like methylphenidate, D-Methylphenidate and Armodafinil have been used with little effect. There are no guidelines to diagnose and / or treat fatigue in Sarcoidosis patients.

In our study we tried to look at the prevalence of Fatigue as a symptom in patients with Sarcoidosis. This study was planned to reiterate the importance of fatigue and the burden of the symptom in Sarcoidosis patients. The tool which was used to study fatigue in them is the Fatigue Assessment Scale which has been validated for assessing fatigue in patients with Sarcoidosis. It has 10 simple questions with a 5 point likert scale of never to always.

Maximum score is 50 and minimum score is 10. Patients whose score is 22 or above is considered to have fatigue. It should be considered as an important symptom in these patients.

We included 75 patients in our study to assess for fatigue. All of them had Pulmonary Sarcoidosis. Histo-pathological diagnosis of Sarcoidosis was present in all of them. Patients who were on treatment and those who were treatment naïve were also included, since the literature review done did not show any difference in fatigue experienced between these 2 groups. After obtaining informed consent in patients own language, FAS score was filled and recorded in the pro-forma for analysis.

We analyzed the data for fatigue in all these patients and multiple variables were studied. The primary objective of the study was to present the prevalence of fatigue in patients with Sarcoidosis. Prevalence of fatigue in our patients was very high at 73.3%. We carefully excluded confounders for fatigue like Anemia, Hypothyroidism, Malignancy and Tuberculosis. Patients whose clinical status could not be differentiated between Sarcoidosis and Tuberculosis who were on therapy for both were also excluded. Patients on steroids may have fatigue secondary to the drug intake and myopathy associated with it. We decided to capture data of dose and duration of steroids which patients have been on since diagnosis and analyze it to see if it was a risk factor for increased fatigue in patients with Sarcoidosis using logistic regression. We also looked at duration since the diagnosis of

Sarcoidosis, if it had any impact on fatigue by comparing the groups who were just started on treatment and those who were on steroids for at least an year.

Prevalence of fatigue which we found was very high in patients who are diagnosed with Sarcoidosis in our institution. 73% of the population with sarcoidosis experience fatigue as a major symptom. It was seen that patients who were on treatment for Sarcoidosis had slightly lesser prevalence of fatigue compared to those who were diagnosed new, suggesting a possibility of fatigue showing minimal improvement with treatment of sarcoidosis. To support the same , patients who were diagnosed 12 months or more and have been on treatment showed lesser prevalence of fatigue compared to those who were treatment naïve or those who were diagnosed within 1 month period. We also looked at patients fatigue in comparison with the dose of steroids they were on, that also did not show any significant difference in the four groups which we studies. We divided patients on steroids into 4 groups depending on the dose of steroids they were on, starting from 0-10mg on one group, followed by 11-19mg in the next, 20-29 in the next group,

CONCLUSION:

We studied patients with sarcoidosis which is a rare disorder. We included 75 patients in our study and assessed the prevalence of fatigue and other extra-pulmonary manifestations.

Prevalence of sarcoidosis is very high, we found the prevalence to be 73.3%, which is in accordance with the studies mentioned in the review of literature. It may be as high as 87.5% in newly diagnosed patients. Since we had patients who were on follow up and patients who were treatment naïve, we assessed the difference between both the groups. In follow up patients prevalence was 66% compared to 87% in the newly diagnosed group). There was no significant difference statistically in age or female sex – odd's ratio of 0.99 and 1.09 respectively in the study, which could be because of the small sample size. A larger study is required to analyse risk factors like age and sex on fatigue in sarcoidosis.

Mainstay of treatment for sarcoidosis is steroids. Steroids may induce myopathy and cause fatigue. We found patients on steroids had 9% higher risk of having fatigue, but statistically it was not found to be significant (odd's ratio; 0.98, p value; 0.752).

Our study reiterates the importance of fatigue as a predominant symptom in patients with sarcoidosis which may be ignored in the clinical setting. Further studies are required to identify therapies which may help patients in treating this symptom. Treatment of fatigue will improve quality of life of the patient which is one of the primary goals of treating patients with sarcoidosis.

We also assessed the same cohort of patients to identify the presence of extra-pulmonary manifestations in them. We strongly recommend minimal initial investigations in a patient

with suspicion or diagnosis of sarcoidosis, to assess for extra-pulmonary manifestation. These investigations are as follows:

- Complete blood count
- Urea and creatinine
- Liver function tests
- Serum and urinary calcium(24 hour)
- ECG
- Eye and Skin screening
- Organ specific history and examination

Above mentioned screening tests were done in all 75 patients and we found the presence of extra-pulmonary manifestations in 45 of them. We observed highest prevalence in Eye and Skin with 26% and 20% respectively. Other organs involved in decreasing order of prevalence were Liver (13%), Bone/Joint/Muscle (10.6%), Spleen (9.3%), Calcium/Kidney (6.6%), Brain (4%), ENT (4%), Heart (1.3%), and Parotid gland (1.3%).

A larger study is required to validate a screening questionnaire for patients with sarcoidosis.

BIBLIOGRAPHY:

1. Criado E, Sánchez M, Ramírez J, Arguis P, de Caralt TM, Perea RJ, et al. Pulmonary sarcoidosis: typical and atypical manifestations at high-resolution CT with pathologic correlation. Radiogr Rev Publ Radiol Soc N Am Inc. 2010 Oct;30(6):1567–86.

2. Sharma SK, Mohan A. Sarcoidosis in India: not so rare. J Indian Acad Clin Med. 2004;5(1):12–21.

3. Rosen Y. Pathology of Sarcoidosis. Semin Respir Crit Care Med. 2007 Feb;28(1):036–52.

4. Mukhopadhyay S, Gal AA. Granulomatous lung disease: an approach to the differential diagnosis. Arch Pathol Lab Med. 2010 May;134(5):667–90.

5. FSR-Physicians-Protocol1.pdf [Internet]. [cited 2013 Oct 21]. Available from: http://www.stopsarcoidosis.org/wp-content/uploads/2013/03/FSR-Physicians-Protocol1.pdf

6. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007 Nov 22;357(21):2153–65.

7. Sarcoidosis. N Engl J Med. 2008 Mar 27;358(13):1402–5.

8. Sarcoidosis: A Primary Care Review - American Family Physician [Internet]. [cited 2013 Oct 21]. Available from: http://www.aafp.org/afp/1998/1201/p2041.html

9. Joshi JM, Saxena S. Sarcoidosis in India. Skin. 2012;11(34):2–20.

10. Gupta SK, Mitra K, Chatterjee S, Chakravarty SC. Sarcoidosis in India. Br J Dis Chest. 1985 Jul;79(3):275–83.

11. Drent M, Lower EE, Vries JD. Sarcoidosis-associated fatigue. Eur Respir J. 2012 Jul 1;40(1):255–63.

12. Aaronson LS, Teel CS, Cassmeyer V, Neuberger GB, Pallikkathayil L, Pierce J, et al. Defining and Measuring Fatigue. Image J Nurs Sch. 1999 Mar 1;31(1):45–50.

13. Drent M, Lower EE, Vries JD. Sarcoidosis-associated fatigue. Eur Respir J. 2012 Jul 1;40(1):255–63.

14. Michielsen HJ, Drent M, Peros-Golubicic T, De Vries J. FAtigue is associated with quality of life in sarcoidosis patients*. Chest. 2006 Oct 1;130(4):989–94.

15. Bush A, Carlsen K-H, Zach M, European Respiratory Society. Growing up with lung disease: the lung in transition to adult life. Sheffield: European Respiratory Society Journals; 2002.

16. De Kleijn WP, De Vries J, Lower EE, Elfferich MD, Baughman RP, Drent M. Fatigue in sarcoidosis: a systematic review: Curr Opin Pulm Med. 2009 Sep;15(5):499–506.

17. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. Eur Respir J. 2012 Jul 1;40(1):255–63.

18. De Vries J, Drent M. Quality of Life and Health Status in Sarcoidosis: A Review. Semin Respir Crit Care Med. 2007 Feb;28(1):121–7.

19. Fatigue in sarcoidosis: a systematic review. [Curr Opin Pulm Med. 2009] - PubMed - NCBI [Internet]. [cited 2013 Oct 6]. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19458531

20. Marcellis RGJ, Lenssen AF, Elfferich MDP, Vries JD, Kassim S, Foerster K, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J. 2011 Sep 1;38(3):628–34.

21. Sharma OP. Fatigue and sarcoidosis. Eur Respir J. 1999;13(4):713–4.

22. De Kleijn WPE, Elfferich MDP, De Vries J, Jonker GJ, Lower EE, Baughman RP, et al. Fatigue in sarcoidosis: American versus Dutch patients. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG World Assoc Sarcoidosis Granulomatous Disord. 2009 Jul;26(2):92–7.

23. Cottin V, Müller-Quernheim J. Sarcoidosis from bench to bedside: a state-of-the-art series for the clinician. Eur Respir J. 2012 Jul 1;40(1):14–6.

24. Vucinic V, Stojkovic M, Milenkovic B, Videnovic-Ivanov J, Skodric-Trifunovic V, Zugic V, et al. Fatigue in sarcoidosis: Detection and treatment. Srp Arh Celok Lek. 2012;140(1-2):104–9.

25. Gvozdenovic BS, Mihailovic-Vucinic V, Ilic-Dudvarski A, Zugic V, Judson MA. Differences in symptom severity and health status impairment between patients with pulmonary and pulmonary plus extrapulmonary sarcoidosis. Respir Med. 2008 Nov;102(11):1636–42.

26. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. Eur Respir J. 2012 Jul 1;40(1):255–63.

27. ******* CIS20R ******* - CIS.pdf [Internet]. [cited 2014 Sep 16]. Available from: http://arni.uk.com/pdf/CIS.pdf

28. Korenromp IHE, Heijnen CJ, Vogels OJM, van den Bosch JMM, Grutters JC. Characterization of chronic fatigue in patients with sarcoidosis in clinical remission. Chest. 2011 Aug;140(2):441–7.

29. De Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). Br J Health Psychol. 2004 Sep;9(Pt 3):279–91.

30. Lower EE, Malhotra A, Surdulescu V, Baughman RP. Armodafinil for Sarcoidosis-Associated Fatigue: A Double-Blind, Placebo-Controlled, Crossover Trial. J Pain Symptom Manage. 2013 Feb;45(2):159–69.

31. Lower EE. Double-Blind, Randomized Trial of Dexmethylphenidate Hydrochloride for the Treatment of Sarcoidosis-Associated Fatigue<xref rid=“AFF1”>[*]</xref> CHEST J. 2008 May 1;133(5):1189.

32. Smets EM, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. J Psychosom Res. 1995 Apr;39(3):315–25.

33. Hinz A, Fleischer M, Brähler E, Wirtz H, Bosse-Henck A. Fatigue in patients with sarcoidosis, compared with the general population. Gen Hosp Psychiatry. 2011 Sep;33(5):462–8.

34. Fleischer M, Hinz A, Brähler E, Wirtz H, Bosse-Henck A. Factors Associated With Fatigue in Sarcoidosis. Respir Care. 2014 Jul 1;59(7):1086–94.

35. Kalkanis A, Yucel RM, Judson MA. The internal consistency of PRO fatigue instruments in sarcoidosis: superiority of the PFI over the FAS. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG World Assoc Sarcoidosis Granulomatous Disord. 2013 Mar;30(1):60–4.

36. Marcellis RGJ, Lenssen AF, Elfferich MDP, De Vries J, Kassim S, Foerster K, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J. 2011 Mar 24;38(3):628–34.

37. Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday Cognitive Failure in Sarcoidosis: The Prevalence and the Effect of Anti-TNF-alpha Treatment. Respiration. 2010;80(3):212–9.

38. Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. J Psychosom Res. 2003 Apr;54(4):345–52.

39. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. Chest. 2007 Jul;132(1):207–13.

40. De Kleijn WPE, De Vries J, Wijnen PAHM, Drent M. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. Respir Med. 2011 Sep;105(9):1388–95.

41. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in acute pulmonary sarcoidosis. [cited 2014 Sep 23]; Available from: http://www.ildcare.eu/Downloads/proefschriften/proefschriften_2004/Thesis_S._Rothkrantz_-_2004_-_Chapter_06.pdf

42. Drent M, Lower EE, De Vries J. Sarcoidosis-associated fatigue. Eur Respir J. 2012 Jul 1;40(1):255–63.

43. Microsoft Word - ERJ-00025-2012_Revision_Review_Sarcoidosis_associated_fatigue_ERJ_Marked_Copy - 09031936.00002512.full.pdf [Internet]. [cited 2014 Sep 15]. Available from: http://erj.ersjournals.com/content/early/2012/03/22/09031936.00002512.full.pdf

44. 0370-81791202104V.pdf [Internet]. [cited 2014 Sep 16]. Available from: http://www.doiserbia.nb.rs/img/doi/0370-8179/2012/0370-81791202104V.pdf

45. Costabel U. Skeletal muscle weakness, fatigue and sarcoidosis. Thorax. 2005 Jan 1;60(1):1–2.

46. Heij L, Dahan A, Hoitsma E. Sarcoidosis and Pain Caused by Small-Fiber Neuropathy. Pain Res Treat. 2012 Dec 5;2012:e256024.

47. - hoitsma_-_2005_-_chapter_05.pdf [Internet]. [cited 2014 Sep 18]. Available from: http://www.ildcare.eu/downloads/proefschriften/proefschriften_2005/hoitsma_-_2005_-_chapter_05.pdf

48. Drent M, Verbraecken J, van der Grinten C, Wouters E. Fatigue associated with obstructive sleep apnea in a patient with sarcoidosis. Respir Int Rev Thorac Dis. 2000;67(3):337–40.

49. Turner GA, Lower EE, Corser BC, Gunther KL, Baughman RP. Sleep apnea in sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG World Assoc Sarcoidosis Granulomatous Disord. 1997 Mar;14(1):61–4.

50. Kleijn_fatigue_16-05-2012.pdf [Internet]. [cited 2014 Sep 15]. Available from: https://pure.uvt.nl/portal/files/1428538/Kleijn_fatigue_16-05-2012.pdf

51. Magnusson AE, Nias DK, White PD. Is perfectionism associated with fatigue? J Psychosom Res. 1996 Oct;41(4):377–83.

52. Sharma OP, Mihailovic-Vucinic V. Lesions of Sarcoidosis. JP Medical Ltd; 2014. 200 p.

53. Marcellis RGJ, Lenssen AF, Elfferich MDP, Vries JD, Kassim S, Foerster K, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. Eur Respir J. 2011 Sep 1;38(3):628–34.

54. De Kleijn WPE, Drent M, Vermunt JK, Shigemitsu H, De Vries J. Types of fatigue in sarcoidosis patients. J Psychosom Res. 2011 Dec;71(6):416–22.

55. Erckens RJ, Mostard RLM, Wijnen P a. HM, Schouten JS, Drent M. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. Graefes Arch Clin Exp Ophthalmol Albrecht Von Graefes Arch Für Klin Exp Ophthalmol. 2012 May;250(5):713–20.

56. Microsoft Word - Fatigue from sarcoidosis treat the cause.doc - Fatigue_from_sarcoidosis_treat_the_cause.pdf [Internet]. [cited 2014 Sep 16]. Available from: http://www.ildcare.eu/Downloads/nieuws/Fatigue_from_sarcoidosis_treat_the_cause.pdf

57. Okumus G, Musellim B, Cetinkaya E, Turker H, Uzaslan E, Yenturk E, et al. Extrapulmonary involvement in patients with sarcoidosis in Turkey: Extrapulmonary sarcoidosis in Turkey. Respirology. 2011 Apr;16(3):446–50.

58. Extrapulmonary Sarcoidosis.pdf [Internet]. [cited 2013 Oct 21]. Available from: http://pneumonologia.gr/articlefiles/Extrapulmonary%20Sarcoidosis.pdf

59. Chapter 10 Skin manifestations in sarcoidosis.pdf [Internet]. [cited 2014 Sep 18]. Available from: http://www.ildcare.eu/Downloads/artseninfo/Sarcoidosis/Chapter%2010%20Skin%20manifestations%20in%20sarcoidosis.pdf

60. Yanardağ H, Pamuk ON, Karayel T. Cutaneous involvement in sarcoidosis: analysis of the features in 170 patients. Respir Med. 2003 Aug;97(8):978–82.

61. Cutaneous Sarcoidosis: A Dermatologic Masquerader - American Family Physician [Internet]. [cited 2014 Sep 18]. Available from: http://www.aafp.org/afp/2002/0415/p1581.html

62. Abu-Hilal M, Krotva J, Chichierchio L, Obeidat N, Madanat M. Dermatologic aspects and cutaneous manifestations of sarcoidosis. G Ital Dermatol E Venereol Organo Uff Soc Ital Dermatol E Sifilogr. 2010 Dec;145(6):733–45.

63. Symptoms of Sarcoidosis [Internet]. [cited 2014 Sep 18]. Available from: https://chronicillnessrecovery.org/index.php?option=com_content&view=article&id=190

64. Grunewald J, Eklund A. Löfgren's Syndrome. Am J Respir Crit Care Med. 2009 Feb 15;179(4):307–12.

65. Mañá J, Marcoval J, Graells J, Salazar A, Peyrí J, Pujol R. Cutaneous involvement in sarcoidosis: Relationship to systemic disease. Arch Dermatol. 1997 Jul 1;133(7):882–8.

66. Reddy RR, Shashi Kumar BM, Harish MR. CUTANEOUS SARCOIDOSIS - A GREAT MASQUERADER: A REPORT OF THREE INTERESTING CASES. Indian J Dermatol. 2011;56(5):568–72.

67. Yanardag H, Tetikkurt C, Bilir M, Demirci S, Iscimen A. Diagnosis of cutaneous sarcoidosis; clinical and the prognostic significance of skin lesions. Multidiscip Respir Med. 2013 Mar 22;8(1):26.

68. Judson MA, Baughman RP, Costabel U, Flavin S, Lo KH, Kavuru MS, et al. Efficacy of infliximab in extrapulmonary sarcoidosis: results from a randomised trial. Eur Respir J. 2008 Jun;31(6):1189–96.

69. Baughman RP, Drent M, Kavuru M, Judson MA, Costabel U, du Bois R, et al. Infliximab therapy in patients with chronic sarcoidosis and pulmonary involvement. Am J Respir Crit Care Med. 2006 Oct 1;174(7):795–802.

70. ocular_sarcoidosis.pdf [Internet]. [cited 2013 Oct 21]. Available from: http://www.uveitis.org/docs/dm/ocular_sarcoidosis.pdf

71. Rothova A. Ocular involvement in sarcoidosis. Br J Ophthalmol. 2000 Jan 1;84(1):110–6.

72. - 234.full.pdf [Internet]. [cited 2014 Sep 18]. Available from: http://aje.oxfordjournals.org/content/145/3/234.full.pdf

73. Rothova A. Ocular involvement in sarcoidosis. Br J Ophthalmol. 2000 Jan 1;84(1):110–6.

74. ocular sarcoid..pdf [Internet]. [cited 2014 Sep 18]. Available from: http://www.med.unc.edu/tarc/events/event-files/ocular%20sarcoid..pdf

75. zotero://attachment/406/ [Internet]. [cited 2014 Sep 19]. Available from: zotero://attachment/406/

76. Judson MA, Baughman RP, Teirstein AS, Terrin ML, Yeager H. Defining organ involvement in sarcoidosis: the ACCESS proposed instrument. ACCESS Research Group. A Case Control Etiologic Study of Sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG World Assoc Sarcoidosis Granulomatous Disord. 1999 Mar;16(1):75–86.

77. Herbort CP, Rao NA, Mochizuki M, members of Scientific Committee of First International Workshop on Ocular Sarcoidosis. International criteria for the diagnosis of ocular sarcoidosis: results of the first International Workshop On Ocular Sarcoidosis (IWOS). Ocul Immunol Inflamm. 2009 Jun;17(3):160–9.

78. zotero://attachment/416/ [Internet]. [cited 2014 Sep 19]. Available from: zotero://attachment/416/

79. Ayyala US, Padilla ML. Diagnosis and treatment of hepatic sarcoidosis. Curr Treat Options Gastroenterol. 2006;9(6):475–83.

80. getpdf.php [Internet]. [cited 2014 Sep 19]. Available from: http://njmonline.nl/getpdf.php?t=a&id=10000876

81. Hepatic Sarcoidosis: Clinicopathologic Features in 100 Patie... : The American Journal of Surgical Pathology [Internet]. [cited 2014 Sep 19]. Available from:

http://journals.lww.com/ajsp/abstract/1993/12000/hepatic_sarcoidosis__clinicopathologic_features_in.9.aspx

82. Warshauer DM, Lee JKT. Imaging Manifestations of Abdominal Sarcoidosis. Am J Roentgenol. 2004 Jan 1;182(1):15–28.

83. Patel I, Ismajli M, Steuer A. Sarcoidosis Presenting as Massive Splenic Infarction. Case Rep Rheumatol. 2012 Jul 30;2012:e834758.

84. zotero://attachment/83/ [Internet]. [cited 2014 Aug 16]. Available from: zotero://attachment/83/

85. Selroos O. Sarcoidosis of the Spleen. Acta Med Scand. 1976 Jan 12;200(1-6):337–40.

86. DELANEY P. Neurologic Manifestations in SarcoidosisReview of the Literature, with a Report of 23 Cases. Ann Intern Med. 1977 Sep 1;87(3):336–45.

87. Neurological complications of sarcoidosis : Current Opinion in Neurology [Internet]. [cited 2014 Sep 19]. Available from: http://journals.lww.com/co-neurology/Fulltext/2004/06000/Neurological_complications_of_sarcoidosis.13.aspx

88. Stern BJ, Krumholz A, Johns C, Scott P, Nissim J. Sarcoidosis and its neurological manifestations. Arch Neurol. 1985 Sep;42(9):909–17.

89. Gullapalli D, Phillips LH. Neurologic manifestations of sarcoidosis. Neurol Clin. 2002 Feb;20(1):59–83, vi.

90. Zajicek JP, Scolding NJ, Foster O, Rovaris M, Evanson J, Moseley IF, et al. Central nervous system sarcoidosis—diagnosis and management. QJM. 1999 Feb 1;92(2):103–17.

91. Christoforidis GA, Spickler EM, Recio MV, Mehta BM. MR of CNS Sarcoidosis: Correlation of Imaging Features to Clinical Symptoms and Response to Treatment. Am J Neuroradiol. 1999 Apr 1;20(4):655–69.

92. Lower EE, Broderick JP, Brott TG, Baughman RP. DIagnosis and management of neurological sarcoidosis. Arch Intern Med. 1997 Sep 8;157(16):1864–8.

93. James DG, Sharma OP. Parotid gland sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis Off J WASOG World Assoc Sarcoidosis Granulomatous Disord. 2000 Mar;17(1):27–32.

94. Fatahzadeh M, Rinaggio J. Diagnosis of systemic sarcoidosis prompted by orofacial manifestations: a review of the literature. J Am Dent Assoc 1939. 2006 Jan;137(1):54–60.

95. Walter C, Schwarting A, Hansen T, Weibrich G. [Heerfordt's syndrome -- a rare initial manifestation of sarcoidosis]. Mund- Kiefer- Gesichtschirurgie MKG. 2005 Jan;9(1):43–7.

96. Harvey J, Catoggio L, Gallagher PJ, Maddison PJ. Salivary gland biopsy in sarcoidosis. Sarcoidosis. 1989 Mar;6(1):47–50.

97. Beeley JA, Chisholm DM. Sarcoidosis with salivary gland involvement: biochemical studies on parotid saliva. J Lab Clin Med. 1976 Aug;88(2):276–81.

98. Çakmak SK, Gönül M, Gül Ü, Gündüz H, Han Ö, Kulaçoğlu S. Sarcoidosis involving the lacrimal, submandibular, and parotid glands with panda sign. Dermatol Online J [Internet]. 2009 Mar 1 [cited 2014 Sep 20];15(3). Available from: https://escholarship.org/uc/item/80j4r407

99. Browne PM, Sharma OP, Salkin D. BOne marrow sarcoidosis. JAMA. 1978 Dec 8;240(24):2654–5.

100. Yanardağ H, Pamuk GE, Karayel T, Demirci S. Bone marrow involvement in sarcoidosis: an analysis of 50 bone marrow samples. Haematologia (Budap). 2002;32(4):419–25.

101. Mostard RL, Prompers L, Weijers RE, van Kroonenburgh MJ, Wijnen PA, Geusens PP, et al. F-18 FDG PET/CT for detecting bone and bone marrow involvement in sarcoidosis patients. Clin Nucl Med. 2012 Jan;37(1):21–5.

102. Prompers L, Mostard R, Weyers R, Drent M, Voo S, van Kroonenburgh M. Assessing bone (marrow) involvement in sarcoidosis using F18-FDG PET/CT. Soc Nucl Med Annu Meet Abstr. 2011 May 1;52(1_MeetingAbstracts):513.

103. Lower EE, Smith JT, Martelo OJ, Baughman RP. The anemia of sarcoidosis. Sarcoidosis. 1988 Mar;5(1):51–5.

104. Milton CM. Sarcoidosis in ENT practice. Clin Otolaryngol Allied Sci. 1985 Dec;10(6):351–5.

105. 20060502_Sinonasal_Sarcoidosis.pdf [Internet]. [cited 2014 Sep 20]. Available from: http://www.pneumonologia.gr/articlefiles/20060502_Sinonasal_Sarcoidosis.pdf

106. CAMA E, SANTARELLI R, MUZZI E, INCHES I, CURTOLO S, DI PAOLA F, et al. Sudden hearing loss in sarcoidosis: otoneurological study and neuroradiological correlates. Acta Otorhinolaryngol Ital. 2011 Aug;31(4):235–8.

107. Internet Scientific Publications [Internet]. [cited 2014 Sep 20]. Available from: http://ispub.com/IJORL/13/1/12797

108. Pierre-Louis B, Prasad A, Frishman WH. Cardiac manifestations of sarcoidosis and therapeutic options. Cardiol Rev. 2009 Aug;17(4):153–8.

109. Chapter 9 Cardiac involvement in sarcoidosis.pdf [Internet]. [cited 2014 Sep 20]. Available from: http://ildcare.eu/Downloads/artseninfo/Sarcoidosis/Chapter%209%20Cardiac%20involvement%20in%20sarcoidosis.pdf

110. Sekhri V, Sanal S, DeLorenzo LJ, Aronow WS, Maguire GP. Cardiac sarcoidosis: a comprehensive review. Arch Med Sci AMS. 2011 Aug;7(4):546–54.

111. Diagnosis and Management of Cardiac Sarcoidosis - cardiac_sarcoidosis.pdf [Internet]. [cited 2013 Oct 21]. Available from: http://www.sarcoidosisonlinesites.com/cardiac_sarcoidosis.pdf

112. Koyama T, Ueda H, Togashi K, Umeoka S, Kataoka M, Nagai S. Radiologic Manifestations of Sarcoidosis in Various Organs1. RadioGraphics. 2004 Jan;24(1):87–104.

113. Chapter 13 Sarcoidosis joint muscle and bone.pdf [Internet]. [cited 2013 Oct 21]. Available from:

http://www.ildcare.eu/Downloads/artseninfo/Sarcoidosis/Chapter%2013%20Sarcoidosis%20joint%20muscle%20and%20bone.pdf

114. Zisman DA, Shorr AF, Lynch JP. Sarcoidosis involving the musculoskeletal system. Semin Respir Crit Care Med. 2002 Dec;23(6):555–70.

115. Moore SL, Teirstein AE. Musculoskeletal Sarcoidosis: Spectrum of Appearances at MR Imaging1. RadioGraphics. 2003 Nov;23(6):1389–99.

116. Conron M, Young C, Beynon HLC. Calcium metabolism in sarcoidosis and its clinical implications. Rheumatology. 2000 Jul 1;39(7):707–13.

117. Rizzato G. Clinical impact of bone and calcium metabolism changes in sarcoidosis. Thorax. 1998 May 1;53(5):425–9.

118. Fowler A, Dargan P, Jones A. Puzzling hypercalcaemia: sarcoidosis without lung involvement. J R Soc Med. 2005 Feb;98(2):60–1.

ANNEXURE:

Proforma:

1. Serial Number:
2. Name:
3. Hospital number:
4. Age:
5. Sex: Male/Female
6. Marital status: Married/ Unmarried
7. Profession:
8. Any exclusion criteria met: Yes / No
9. Informed consent obtained: Yes / No
10. Kindly answer Yes/No to the following questions:

    a. Diagnosed with Pulmonary Sarcoidosis : Yes/ No

    Histopathological Diagnosis: Yes / No

    New / Old patient:

    Duration since diagnosis:

    b. On treatment for Sarcoidosis : Yes / No – If Yes, answer following:

        1. On steroids:
        2. Current dose of steroids:
        3. Duration of treatment:
        4. Other treatment/Duration:

    c. If Subjective symptom of fatigue present: Yes / No

Fatigue assessment score completed: Yes / No
FAS Score:

d. Any skin manifestation : Yes / No – If Yes, Circle: Lupus pernio/ Maculopapular lesions/Annular lesion/Erythema nodosum/Others

e. Ocular manifestation: Yes / No – If Yes, Circle: Anterior uveitis/Posterior uveitis/Retinal Vasculitis/Kerataconjunctivitis/Others

f. Liver involvement: Yes / No – If Yes, Circle: Elevated Liver enzymes/ Hepatomegaly/ granulomas In liver biopsy/Others

g. Spleen involevement: Yes / No – If Yes, Circle: Splenomegaly / Splenic infarcts / Others

h. Brain involvement :Yes / No – If Yes, Circle: cranial-nerve palsies/headache/ataxia/cognitive dysfunction/ seizures/others

i. Parotid/salivary gland involvement: Yes / No

j. Bone marrow involvement: Yes / No – If Yes, Circle: Anemia, Leucopenia/Thrombocytopenia/ Bone marrow biopsy with granulomas/Others

k. ENT Involvement: Yes / No – If Yes, Circle: Hearing Loss/ Nasal obstruction/Rhinorrhea

l. Cardiac manifestation: Yes / No – If Yes, Circle: Arrhythmias/Conduction blocks/ Others

m. Bone/Joint/Muscle involvement: Yes / No – If Yes, Circle: Arthralgia/Arthritis/Myopathy/Others

n. Calcium/Renal involvement: Yes / No – If Yes, Circle: Hypercalcemia /Hypercalciuria/Others

Information sheet:

Study title

To calculate the number of people suffering with the symptom of fatigue in all patients diagnosed to have a disease called as Sarcoidosis .

Invitation paragraph

'You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully'.

What is the purpose of the study?

It has been seen that the symptom of Fatigue is incompletely understood and treated, hence this study will try to reinstate the importance of fatigue in patients suffering with Sarcoidosis. And will also capture the prevalence of other organ involvement in Sarcoidosis.

Why have I been invited to participate?

You have been invited to participate in the study since you have been diagnosed with Sarcoidosis and that your valuable time in filling the questionnaire will help physicians worldwide to understand the importance of fatigue. A minimum of 50 patients are required for us to complete the study, therefore we will require another 49 patients like you with the same diagnosis will be enrolled.

Do I have to take part?

'It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason'.

What will happen to me if I take part?

You will be asked to fill in a questionnaire with 10 simple questions , where you will be asked to grade from 1 to 5 for all the questions, at the end a score will be calculated to assess if you are experiencing symptoms of fatigue. It will take around 10 to 15min of your valuable time. Your blood and other results will be seen to look for oragns other than lung involvement in you for analysing the final data for the study. All data collected will be strictly confidential and it will be stored and analysed for research purposes in the coming time. All details will be stored as an electronic and paper copy. You don’t have to pay anything to take part in the study.

What should I do if I want to take part?

You will have to sign the consent form attached to this information sheet and fill in the Fatigue Assesment Scale questionnaire which will be given to you as described earlier.

What will happen to the results of the research study?

The results of this study will be analysed and submitted as a part of my Thesis and if approved will be published for the interest of the medical fraternity. There are no added risks associated with this study. You may have to spend approximately 5-15 min extra to participate in this study as explained earlier.

Your details will be kept confidential and will not be disclosed with any one who is not associated with the study. Your participation in this study is entirely voluntary and you are also free to decide to withdraw permission to participate in this study. If you do so, this will not affect your usual treatment at this hospital in any way.

The results of this study will be published in a medical journal but you will not be identified by name in any publication or presentation of results. However, your medical notes may be reviewed by people associated with the study, without your additional permission, should you decide to participate in this study.

Who is organising and funding the research?

This study is being organised by the Department of Pulmonary Medicine, Christian Medical College, Vellore and funded by the Christian Medical College, Vellore.

Who has reviewed the study?

This study has been reviewed by the Institutional Review Board, Christian Medical College, Vellore.

Contact for Further Information

You are free to contact the principal investigator of the study for any doubts at the following contact information provided..

We thank you for taking time to read the information sheet.

Date:

Consent From:

CONSENT FORM

Full title of Project: To Calculate the Prevalence of Fatigue in patients diagnosed with Sarcoidosis with the help of Fatigue Assessment Scale and to present the observed prevalence of other extra-pulmonary manifestations .

Name, position and contact address of Researcher: Dr.Immanuel Subash.G, PG registrar, CMC Vellore, Tamil Nadu

Subject's Initials: _____ Subject's Name: _____
Date of Birth / Age:_____

		Please tick box(subject)
(i)	I confirm that I have read and understood the information sheet for the above study and have had the opportunity to ask questions.	[ ]
(ii)	I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	[ ]
(iii)	I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.	[ ]
(iv)	I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s)	[ ]

(v)	I agree to take part in the above study	[ ]

Signature/Thumb print of the Subject/Legally Acceptable Representative:_____
Date: _____/_____/_____
Signatory's Name: _____

Signature of the Investigator: _____
Date: _____/_____/_____
Study Investigator's Name: Dr. Immanuel Subash.G

Signature/Thumb print and name of the Witness: _____
Date:_____/_____/_____
Name of the Witness: _____

Patient data sheet:

id	name	h	age	sex	marital	occupation	exclusion	consent	diagnosis	hp	status	duration	treatment	steroids
1	dilip kumar yadav	205177f	47	1	TRUE	professor	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
2	lakshmi p	835240f	43	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
3	raghavendra kumar mishra	710372f	47	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
4	sumita paul	826076f	39	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
5	ashok bagaria	872761f	50	1	TRUE	business	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
6	abdul razzak	319317d	52	1	TRUE	driver	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
7	mahmuda aktar	979493a	42	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
8	jayanthi k	867199f	54	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
9	muneshwari devi	770720f	61	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
10	md zamil ansari	261074f	43	1	TRUE	teacher	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
11	erica baruah n d	860948f	44	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
12	lakshman jha	862316f	44	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
13	aruna	467340f	57	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	3	TRUE	TRUE
14	basudeb karmakar	525440b	46	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
15	chandra nand	775779f	52	1	TRUE	teacher	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
16	tapan dey	949808c	61	1	TRUE	service	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
17	samir ranjan patra	794619c	52	1	TRUE	teacher	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
18	ganesh chandra mitra	758351d	56	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
19	suppathal	067591f	67	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
20	md rajwan mia	161932f	40	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	2	3	TRUE	TRUE
21	sankar kumar biswas	208563	36	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
22	anil kumar sinha	226999f	44	1	TRUE	service	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
23	urmila devi	093435f	50	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
24	nur fatima begum	420208f	45	2	TRUE	teacher	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
25	sohan lal jain	264263f	57	1	TRUE	businessman	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
26	fr antony thomas	745192f	48	1	FALSE	pastor	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
27	rachita banerjee	436416f	40	2	TRUE	engineer	FALSE	TRUE	TRUE	TRUE	2	3	TRUE	TRUE

28	beulah sarojini	019665a	65	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
29	bijoy kumar pramanik	427167f	38	1	TRUE	businessman	FALSE	TRUE	TRUE	TRUE	2	3	TRUE	TRUE
30	arun kundu	809171f	45	1	TRUE	fridge dealer	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
31	samrat deb	400516f	27	1	FALSE	student	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
32	nomita ghosh	397414f	31	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
33	rajesh kumar	410907f	43	1	TRUE	scientist	FALSE	TRUE	TRUE	TRUE	2	3	TRUE	TRUE
34	shanthia k	184695f	53	2	TRUE	nurse	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
35	barna das	431966f	25	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
36	indra kumari	607454f	50	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
37	indu devi	297427f	50	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
38	milton amos	682899f	81	1	TRUE	retired officer	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
39	pritpal singh	672097d	52	1	TRUE	businessman	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
40	preetha ramesh	054941c	40	2	TRUE	teacher	FALSE	TRUE	TRUE	TRUE	2	3	TRUE	TRUE
41	md saiful islam	871688f	41	1	TRUE	labourer	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
42	minu kumari	868877f	48	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
43	shankuntala patra	256078f	51	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
44	samir kumar bhadra	722165d	54	1	TRUE	service	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
45	rajkumari	653157c	62	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
46	kumaraswamy raju	083114f	62	1	TRUE	retired principal	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
47	ram kishan jaiswal	488181d	30	1	TRUE	service	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
48	asha devi	302560c	49	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
49	sanjib das	912941f	32	1	TRUE	teacher	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
50	boaraiah	784651f	64	1	TRUE	retired	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
51	subhajit mannaka	912575f	21	1	FALSE	student	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
52	koly begum	869341f	42	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
53	shamshun nahar	208621f	45	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
54	jamal ara	789034f	48	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
55	ravindra prakash	017579g	46	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
56	beni madhav jha	012748g	52	1	TRUE	government service	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
57	laxmi devi	262533d	51	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
58	mayank chaturvedi	020981f	53	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
59	saravanan	995374d	43	1	TRUE	engineer	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
60	vishwanath harihar an	693587f	31	1	TRUE	engineer	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
61	rekha kumari	653245f	47	2	TRUE	house wife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
62	bijay kumar	152551f	43	1	TRUE	service	FALSE	TRUE	TRUE	TRUE	2	2	TRUE	TRUE

63	aggarwal gurusw amy k	293867 f	47	1	TRUE	bill collector	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
64	utpal mukherjee	602289 f	36	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	2	2	TRUE	TRUE
65	mani bhushan prasad	603072 f	48	1	TRUE	businessman	FALSE	TRUE	TRUE	TRUE	2	2	TRUE	TRUE
66	abha gupta	477672 f	40	2	TRUE	housewife	FALSE	TRUE	TRUE	TRUE	2	2	TRUE	TRUE
67	indu devi garodia	693755 f	40	2	TRUE	housewife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
68	john t u	727928 f	55	1	TRUE	manager	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE
69	sudhanshu sekhar	039175 d	59	1	TRUE	clerk	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
70	kiran devi agarwal	259273 d	54	2	TRUE	housewife	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
71	manoj kumar jaiswal	385934 f	43	1	TRUE	businessman	FALSE	TRUE	TRUE	TRUE	2	4	TRUE	TRUE
72	renu devi	103820 d	51	2	TRUE	housewife	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
73	rikeba devi	397430 f	61	2	TRUE	housewife	FALSE	TRUE	TRUE	TRUE	1	3	FALSE	FALSE
74	sabitha singh	954543 c	45	2	TRUE	housewife	FALSE	TRUE	TRUE	TRUE	2	4	FALSE	FALSE
75	fazeela nausha d	613640 f	34	2	TRUE	housewife	FALSE	TRUE	TRUE	TRUE	1	1	FALSE	FALSE

dose	treatment1	other	fatigue	fas	score	skin	type	eye	type1	liver	type2	spleen	type3	brain
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